A NOVEL SYNTHESIS OF ISOQUINOLINES CONTAINING AN ELECTRON WITHDRAWING SUBSTITUENT

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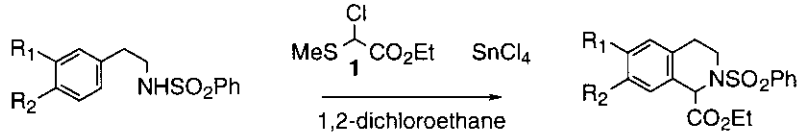
Abstract - 3,4-Dihydroisoquinolines (**10, 13**) and isoquinolines (**11**), having various electron withdrawing substituent were synthesized in two steps from *N*-benzenesulfonyl- or *N,N*-dimethylsulfamoyl-*β*-phenethylamines (**2** and **5**). A novel cyclization method using ethyl chloro(methylthio)acetate (**1**) in the presence of $SnCl_4$ as Lewis acid, followed by acid or base treatment provides the title compounds in good yield.

Various substituted isoquinolines have been frequently synthesized and applied to syntheses of natural products as well as in medicinal chemistry.[1] However, it is well known that the synthesis of isoquinolines containing electron withdrawing substituent by using classical cyclization methodologies, such as Bischler-Napieralski reaction,[2] Pomeranz-Fritsch reaction,[3] Pictet-Spengler reaction[4] and so on, is difficult. These cyclization reactions occur only when the benzene ring is activated by electron donating substituents. Modified methods are reported in which the authors performed cyclizations by increasing the electrophilicity of iminium group by means of an electron withdrawing substituent, such as acyl[5-7] or sulfonyl[7-9] group on the nitrogen. *β*-Phenethylamines bearing an electron withdrawing substituent on the benezene ring afford 1,2,3,4-tetrahydroisoquinoline derivatives in poor yields or do not give any cyclized product.

Previously, we[10] reported that the reaction of *N*-benzenesulfonyl-*β*-phenethylamines (**2**) with ethyl chloro(methylthio)acetate (**1**) in the presence of $SnCl_4$ afford the ethyl *N*-benzenesulfonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylates (**3**) in good yields. This cyclization proceeds only when H and/or

an electron withdrawing substituent is present on the benzene ring of the *N*-benzensulfonyl-β-phenethylamines. In this paper, we optimized the cyclization conditions and extended them to a novel synthesis of *N*-protected isoquinolines, which provided the isoquinoline after subsequent deprotection of *N*-sulfonyl group and decarboxyalkylation of ester group. We also examined the reaction mechanism by using Et_3SiH reduction of the iminium intermediate.

As shown in Table I, treatment of **2a, b, c** with 1.2 eq. of **1** in the presence of $SnCl_4$ (2.2 eq.) in refluxing 1,2-dichloroethane gave **3a, b** in good yields. The poor yield of the acetyl derivative **3c** (entry 3) was greatly improved (from 44% to 79%, entry 4) when 2.3 equivalents of **1** were employed.

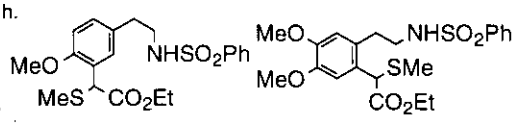


2a~g **3a~g**

Table I. The Reaction of *N*-Benzenesulfonyl-β-phethylamine (**2a-g**) with Ethyl Chloro(methylthio)acetate (**1**).[a]

entry		R_1	R_2	Temp.	**1** (eq.)	$SnCl_4$ (eq.)	Products [yield %][b]		
1	**2a**	H	H	reflux	1.2	2.2	**3a**	91	
2	**2b**	H	F	reflux	1.2	2.2	**3b**	78 (22)[c]	
3	**2c**	H	COMe	reflux	1.2	2.2	**3c**	44 (22)[c]	
4	**2c**	H	COMe	reflux	2.3	2.2	**3c**	79	
5	**2d**	H	CO_2Me	reflux	2.3	2.2	**3d**	97	
6	**2e**	H	NO_2	reflux	2.3	2.2	**3e**	93	
7	**2f**	H	OMe	rt	1.2	2.2	**3f**	N. D.[d]	**4f** 100%
8	**2g**	OMe	OMe	0°C[e]	1.1	1.1	**3g**	30	**4g** 67%

a) The reaction was carried out in 1,2-dichloroethane for 1.5 h.
b) All compounds gave satisfactory spectral data.
c) Yield of recovered starting material
d) N. D. = not detected
e) The reaction was carried out in dichloromethane for 0.5 h.

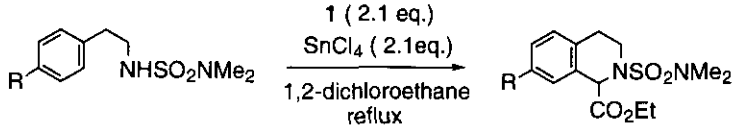


4f **4g**

We also applied these reaction conditions to the 4-methoxycarbonyl derivative (**2d**) which was converted to **3d** in 97% yield (entry 5). Noteworthy are the excellent yields obtained, even in the presence of the strong

electron withdrawing NO_2 group (entry 6). On the other hand, reaction of the electron rich **2f** afforded only Friedel-Crafts product (**4f**) in quantitative yield, as we mentioned before (entry 7). [10] The 3,4-dimethoxy derivative (**2g**) gave a mixture of the cyclized product (**3g**, 30%) and the Friedel-Crafts product (**4g**, 67%) (entry 8).

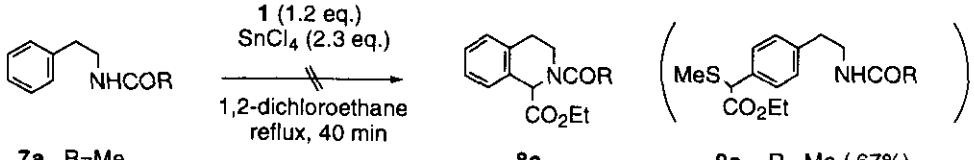
We next examined substituent effects on nitrogen atom of β-phenethylamines in this cyclization reaction. The *N,N*-dimethylsulfamoyl derivatives (**5a, b, c**) were treated under the similar conditions to afford the cyclized products (**6 a, b, c**) in 66, 69, and 73% yields, respectively (Scheme 1). On the contrary, the *N*-acetyl (**7a**) and the *N*-trifluoroacetyl (**7b**) derivatives when treated under similar conditions only afforded the Friedel-Crafts type products (**9a, b**) in good yields. In case of the *p*-NO_2 substituted derivatives (**7c, d**), the desired **8c, d** were not obtained and only starting materials were recovered (Scheme 2). These results point out the importance of the $NHSO_2$ group for this cyclization reaction.



5a R = H
5b R = F
5c R = NO_2

6a 66%
6b 69%
6c 73%

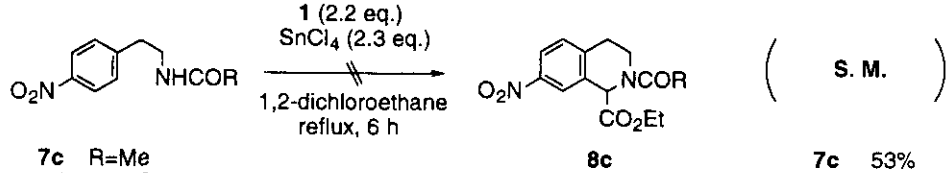
Scheme 1



7a R=Me
7b R=CF_3

8a
8b

9a R= Me (67%)
9b R=CF_3 (66 %)



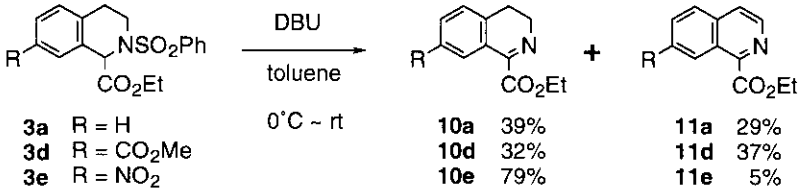
7c R=Me
7d R=CF_3

8c
8d

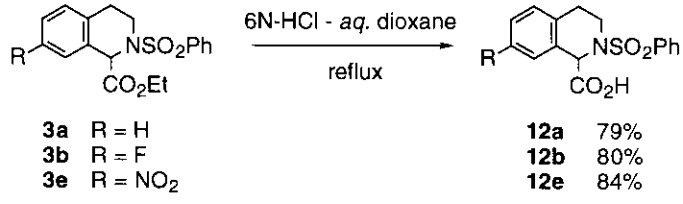
7c 53%
7d 97%

Scheme 2

Since the removal of *N*-tosyl group by using acid or base has been well studied in the isoquinoline chemistry,[11] we next examined the deprotection of the *N*-benzenesulfonyl or *N,N*-dimethyl- sulfamoyl group of **3** and **6** under various acidic or basic conditions. Benzenesulfonyl deprotection of **3a**, **d**, **e** was achieved by using DBU as base, in toluene at 0°C~room temperature, to afford 3,4-dihydroisoquinolines (**10 a**, **d**, **e**) in 39, 32, and 79% yields, accompanied with isoquinolines (**11a**, **d**, **e**) in 29, 37, and 5% yields, respectively (Scheme 3). Under the present method, 1-ethoxycarbonyl group of isoquinolines (**10** and **11**) remained intact. The other basic conditions, such as triethylamine, 4-dimethylaminopyridine in CH_2Cl_2, and *aqueous* alkaline system (NaOH in *aq.* EtOH *etc.*), were less successful. Acidic hydrolysis of **3a**, **b**, **e** in refluxing dioxane only afforded the corresponding carboxylic acid derivatives (**12a**, **b**, **e**) in 79, 80, and 84% yields respectively, in which no desired desulfonylation reaction was observed (Scheme 4).



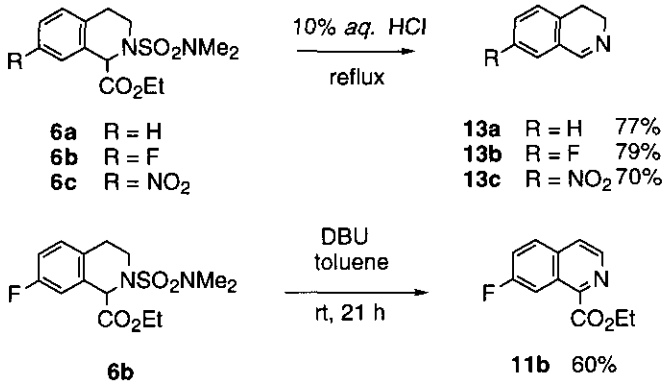
Scheme 3



Scheme 4

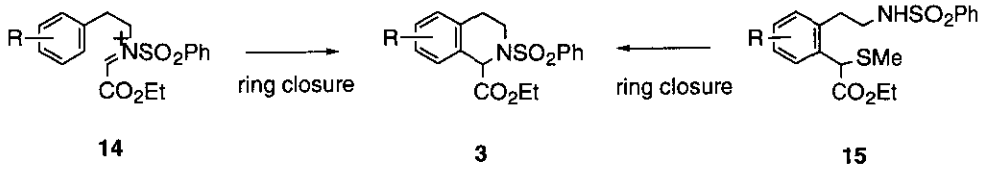
On the other hand, when *N,N*-dimethylsulfamoyl derivatives (**6a-c**) were refluxed in 10% *aq.* HCl, both the decarboxyalkylation of ester group and the deprotection of sulfamoyl group occurred to afford 3,4-dihydroisoquinolines (**13a-c**) in 77, 79, and 70% yields, respectively (Scheme 5). Furthermore, DBU treatment of *N,N*-dimethylsulfamoyl derivative (**6b**) afforded ethyl 7-fluoroisoquinoline-1-carboxylate (**11b**) in 60% yield. A novel synthesis of isoquinolines containing an electron withdrawing group was demonstrated. The two steps involved are Pictet-Spengler cyclization reaction using ethyl chloro-

(methylthio)acetate (**1**) in presence of $SnCl_4$ and a simple acid or base treatment.

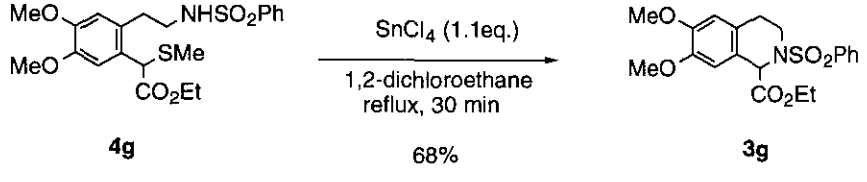


Scheme 5

Two possible pathways for the cyclization reaction are proposed in Scheme 6; the alkylation reaction on the nitrogen of *N*-benzenesulfonyl derivative (**2**) may occur first and be followed by ring closure *via* the iminium intermediate (**14**). Alternatively, Friedel-Crafts alkylation reaction on the benzene ring may proceed first and be followed by ring closure *via* **15**. Actually, the alkylated derivative (**4g**) was easily cyclized to afford **3g** in 68% yield by treatment with $SnCl_4$ in refluxing 1,2-dichloroethane (Scheme 7).



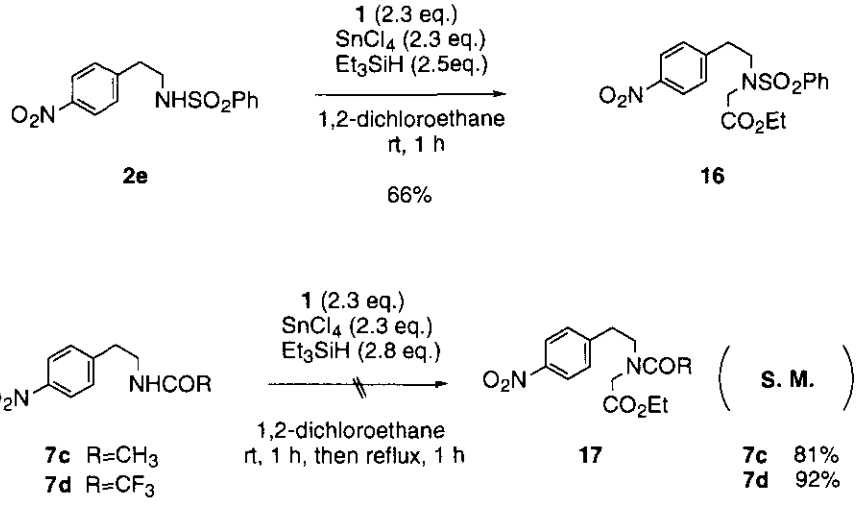
Scheme 6



Scheme 7

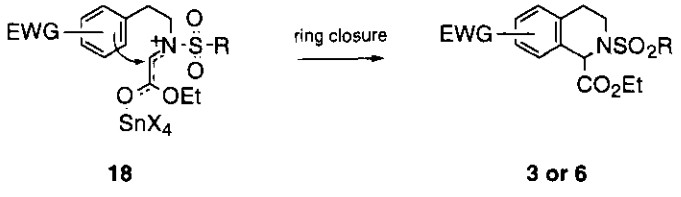
However, this cyclization reaction proceeds predominantly only when a weaker Lewis acid is employed

and H and/or an electron withdrawing group was substituted on the phenyl moiety (this cyclization depends upon the electron density of the benzene ring and the acidity of Lewis acid; see Table I and ref. 10). Since these results suggest the possibility of ring closure *via* the iminium intermediate (**14**), we examined the triethylsilane reduction to trap the reaction intermediate. The treatment of **2e**, $SnCl_4$ (2.3 eq.) and **1** (2.3 eq.) with Et_3SiH (2.5 eq.) in 1,2-dichloroethane at room temperature afforded the *N*-alkylated product (**16**) in 66% yield. But, the acyl amide derivatives (**7a, b**) were treated under similar Et_3SiH reduction condition, no reductive alkylation product (**17**) was obtained even at reflux temperature (Scheme 8).[12] These results suggest that this cyclization proceeds through the formation of iminium intermediate (**14**) followed by subsequent ring closure.



Scheme 8

In this reaction, we speculate that both electron withdrawing sulfonyl group and ester group activate the iminium cation carbon of **18** enough to subject the electrophilic attack of the electron deficient benzene ring (Scheme 9).



Scheme 9

EXPERIMENTAL

Melting points were determined with a Buchi 535 digital melting point apparatus. All melting points are uncollected. IR spectra were obtained with a Analect FT-IR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR were measured with a Varian Gemini-300 spectrometer. All chemical shifts are reported in ppm downfield from tetramethylsilane. MS spectra were recorded with a Hitachi RMU-6 or JEOL JMS-HX 100 mass spectrometer. Silica gel 60N (Kanto chemical) was used for column chromatography. All starting materials were identified with physical data.

Reaction of *N*-Benzenesulfonyl- or *N,N*-Dimethylsulfamoyl-*β*-phenethylamines (2a-g, 5a-c) with Ethyl Chloro(methylthio)acetate (1) and $SnCl_4$ (Table I and Scheme 1).

General Procedure. $SnCl_4$ (0.75 mL, 6.4 mmol) was added to a stirred solution of *N*-benzenesulfonamide-*β*-phenethylamine (**2**) (3.0 mmol) and ethyl chloro(methylthio)acetate (**1**) (1.12 g, 6.3 mmol) in 1,2-dichloroethane (10 mL) at rt. The reaction mixture was refluxed for 1.5 h. After cooling, the reaction mixture was poured into ice-water and extracted with AcOEt. The AcOEt extract was washed with water, sat. *aq.*$NaHCO_3$, and sat. brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on SiO_2 with n-hexane - AcOEt (7 : 3, v/v) as eluant to give the product (**3a~g, 6a~c, 4f** and **4g**).

3a: mp 61~62°C (AcOEt - n-hexane), yield 91%. IR (nujol) cm^{-1}: 1741; MS (ESI) *m/z*: 363 $[M+NH_4]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.15 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.86~2.92 (2H, m, C^4-H), 3.84 (2H, dd, *J* = 7.5, 4.9 Hz, C^3-H), 3.91~4.09 (2H, m, $OC\underline{H}_2CH_3$), 5.54 (1H, s, C^1-H), 7.09~7.12 (1H, m, Aromatic H), 7.18~7.24 (2H, m, Aromatic H), 7.38~7.41 (1H, m, Aromatic H), 7.45~7.58 (3H, m, Aromatic H), 7.82~7.87 (2H, m, Aromatic H); ^{13}C-NMR ($CDCl_3$) δ 13.93, 28.43, 40.96, 57.95, 61.71, 126.79, 127.37, 127.64, 128.16, 129.22, 129.35, 130.13, 132.91, 134.23, 139.89, 170.51. *Anal.* Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H,5.54; N, 4.05; S, 9.28. Found: C, 62.49; H, 5.49; N, 4.02; S, 9.24.

3b: colorless prisms, mp 92.5~93°C (AcOEt - n-hexane), yield 78%. IR (nujol) cm^{-1}:1725; MS (ESI) *m/z*: 386 $[M+Na]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.17 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 2.80~2.88 (2H, m, C^4-H), 3.73~4.08 (4H, m, C^3-H and $OC\underline{H}_2CH_3$), 5.52 (1H, s, C^1-H), 6.93 (1H, dt, *J* = 8.5, 2.6 Hz, C^6-H), 7.07 (1H, dd, *J* = 8.5, 5.7 Hz, C^5-H), 7.13 (1H, dd, *J* = 9.5, 2.6 Hz, C^8-H), 7.46~7.59 (3H, m, Aromatic H), 7.82~7.85 (2H, m, Aromatic H); ^{13}C-NMR ($CDCl_3$) δ: 13.93, 27.71, 40.89, 57.72 (d, *J* =

2.3 Hz), 61.96, 114.27 (d, J = 22.9 Hz), 115.50 (d, J = 21.5 Hz), 127.34, 129.28, 129.85 (d, J = 3.2 Hz), 130.89 (d, J = 8.0 Hz), 131.69 (d, J = 7.5 Hz), 133.04, 139.83, 161.38 (d, J = 245.6 Hz), 169.95. *Anal.* Calcd for $C_{18}H_{18}NO_4FS$: C, 59.49; H, 4.99; N, 3.85; F, 5.23; S, 8.82. Found: C, 59.46; H, 4.93; N, 3.83; F, 5.20; S, 8.86.

3c: pale yellow oil, yield 79%. IR (nujol) cm^{-1}: 1740, 1680; MS (FAB) *m/z*: 388 $[M+H]^+$; High MS (FAB) *m/z*: Calcd for $C_{20}H_{22}NO_5S$: 388.1219, Found: 388.1224 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.17 (3H, t, J = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.58 (3H, s, $COC\underline{H}_3$) 2.85~3.03 (2H, m, C^4-H), 3.77~3.95 (2H, m, C^3-H), 3.96~4.08 (2H, m, $OC\underline{H}_2CH_3$), 5.62 (1H, s, C^1-H), 7.21 (1H, d, J = 8.1 Hz, C^5-H), 7.46~7.60 (3H, m, Aromatic H), 7.79~7.86 (3H, m, Aromatic H), 8.02 (1H, d, J = 1.8 Hz, C^8-H); ^{13}C-NMR ($CDCl_3$) δ 13.96, 26.58, 28.61, 40.47, 57.72, 61.98, 127.37, 127.85, 127.97, 129.30, 129.80, 130.65, 133.09, 135.92, 139.77, 170.01, 197.50.

3d: pale amber oil, yield: 97%. IR (neat) cm^{-1}: 1720; MS (FAB) *m/z*: 404 $[M+H]^+$; High MS (FAB) *m/z*: Calcd for $C_{20}H_{22}NO_6S$: 404.1168, Found: 404.1165 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.17 (3H, t, J =7.1 Hz, $CH_2C\underline{H}_3$), 2.84~3.02 (2H, m, C^4-H), 3.77~3.95 (2H, m, C^3-H), 3.91 (3H, s, $CO_2C\underline{H}_3$), 3.96~4.08 (2H, m, $C\underline{H}_2CH_3$), 5.60 (1H, s, C^1-H), 7.18 (1H, d, J = 8.1 Hz, C^5-H), 7.46~7.59 (3H, m, Aromatic H), 7.82~7.89 (3H, m, Aromatic H), 8.10 (1H, dd, J = 0.9, 0.4 Hz, C^8-H); ^{13}C-NMR ($CDCl_3$) δ 13.94, 28.58, 40.52, 52.28, 57.73, 61.95, 127.37, 128.93, 129.12, 129.29, 129.60, 130.52, 133.06, 139.54, 139.77, 166.76, 170.02.

3e: colorless prisms, mp 87.0~88.5°C (AcOEt - n-hexane), yield 93%. IR (nujol) cm^{-1}: 1734; MS (ESI) *m/z*: 408 $[M+NH_4]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.19 (3H, t, J = 7.3 Hz, $CH_2C\underline{H}_3$), 2.88~3.09 (2H, m, C^4-H), 3.78 (1H, ddd, J = 13.2, 10.3, 4.6 Hz, C^3-H), 3.96~4.13 (3H, m, C^3-H and $C\underline{H}_2CH_3$), 5.67 (1H, s, C^1-H), 7.30 (1H, d, J = 8.4 Hz, C^5-H), 7.48~7.62 (3H, m, Aromatic H), 7.84~7.88 (2H, m, Aromatic H), 8.08 (1H, dd, J = 8.4, 2.4 Hz, C^6-H), 8.33 (1H, d, J = 2.4 Hz, C^8-H). *Anal.* Calcd for $C_{18}H_{18}N_2O_6S$: C, 55.38; H, 4.65; N, 7.18; S, 8.21. Found: C, 55.31; H, 4.56; N, 7.11; S, 7.97.

4f: colorless oil, yield quant. IR (neat) cm^{-1}: 3280, 1730; MS (DI-EI) *m/z*: 423 $[M]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 2.13 (3H, s, SCH_3), 2.70 (2H, t, J =7.0Hz, $ArC\underline{H}_2CH_2N$), 3.17~3.24 (2H, m, $ArCH_2C\underline{H}_2N$), 3.82 (3H, s, OCH_3), 4.14~4.24 (2H, m, $OC\underline{H}_2CH_3$), 4.46 (1H, t-like), 4.89 (1H, s, $C\underline{H}SCH_3$), 6.78 (1H, d, J = 8.4 Hz, C^5-H), 6.99 (1H, dd, J = 8.4, 2.3 Hz, C^6-H), 7.25 (1H, d, J = 2.3 Hz, C^2-H), 7.47~7.57 (3H, m, Aromatic H), 7.81~7.84 (2H, m, Aromatic H).

3g: colorless prisms, mp 77~79°C (AcOEt - n-hexane), yield 30%. IR (nujol) cm^{-1}: 1726; MS (APCI) *m/z*: 406 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.16 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 2.71~2.84 (2H, m, C^4-H), 3.74~3.96 (2H, m, C^3-H), 3.84, 3.85(each 3H, s, OMe), 4.01 (2H, dq, J = 7.1, 2.8 Hz, $OC\underline{H}_2CH_3$), 5.45 (1H, s, C^1-H), 6.56 (1H, s, C^5-H), 6.89 (1H, s, C^8-H), 7.46~7.58 (3H, m, Aromatic H), 7.82~7.85 (2H, m, Aromatic H); ^{13}C-NMR ($CDCl_3$) δ 14.01, 27.95, 40.90, 55.98, 56.09, 57.51, 61.62, 110.21, 111.65, 121.65, 126.46, 127.34, 129.22, 132.90, 139.99, 147.99, 149.06, 170.62. *Anal.* Calcd for $C_{20}H_{23}NO_6S$: C, 59.24; H, 5.72; N, 3.45; S, 7.91. Found: C, 59.17; H, 5.76; N, 3.37; S, 8.14.

4g: colorless caramel, yield 67%. IR (neat) cm^{-1}: 3281, 1732; MS (ESI) *m/z*: 471 $[M+NH_4]^+$; ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.10 (3H, s, SCH_3), 2.85~2.90 (2H, m, $ArC\underline{H}_2CH_2N$), 3.25 (2H, q, *J* = 6.6 Hz, $ArCH_2C\underline{H}_2N$), 3.80, 3.86 (each 3H, s, OCH_3), 4.09~4.25 (2H, m, $OC\underline{H}_2CH_3$), 4.66 (1H, s, $C\underline{H}SCH_3$), 4.87 (1H, t-like, D_2O exchangeable, $N\underline{H}SO_2$), 6.53 (1H, s, Aromatic H), 7.08 (1H, s, Aromatic H), 7.45~7.59 (3H, m, Aromatic H), 7.79~7.82 (2H, m, Aromatic H).

6a: colorless oil, yield 66%. IR (neat) cm^{-1}: 1740; MS (ESI) *m/z*: 330 $[M+NH_4]^+$, 313 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.28 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.80 (6H, s, NMe_2), 2.84~3.08 (2H, m, C^4-H), 3.80~3.89 (2H, m, C^3-H), 4.20 (2H, dq, *J* = 7.1, 0.92 Hz, $OC\underline{H}_2CH_3$), 5.40 (1H, s, C^1-H), 7.14~7.25 (3H, m, Aromatic H), 7.43~7.46 (1H, m, Aromatic H).

6b: pale yellow oil, yield 69%. IR (neat) cm^{-1}: 1740; MS (FAB) *m/z*: 331 $[M+H]^+$; High MS (FAB) *m/z*: Calcd for $C_{14}H_{20}N_2O_4FS$: 331.1116, Found: 331.1128 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.30 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.78~2.85 (1H, m, C^4-H), 2.80 (6H, s, NMe_2), 2.94~3.03 (1H, m, C^4-H), 3.74~3.86 (2H, m, C^3-H), 4.22 (dq, *J* = 7.1, 1.1 Hz, $OC\underline{H}_2CH_3$) 5.34 (1H, s, C^1-H), 6.95 (1H, dt, *J* = 8.6, 2.6 Hz, C^6-H), 7.13 (1H, dd, *J* = 8.6, 5.7 Hz, C^5-H), 7.17 (1H, dd, *J* = 9.3, 2.7 Hz, C^8-H). ^{13}C-NMR ($CDCl_3$) δ: 14.13, 27.79, 38.07, 41.86, 58.48, 58.51, 62.01, 114.50 (d, *J* = 22.9 Hz), 115.44 (d, *J* = 21.5 Hz), 130.12 (d, *J* = 3.2 Hz), 130.89 (d, *J* = 7.7 Hz), 131.95 (d, *J* = 7.4 Hz), 161.39 (d, *J* = 245.6 Hz), 170.67.

6c: pale orange prisms, mp 105~106.5°C (AcOEt - n-hexane), yield 73%. IR (nujol) cm^{-1}: 1727; MS (APCI) *m/z*; 358 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.31 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.83 (6H, s, NMe_2), 2.88~2.96 (1H, m, C^4-H), 3.10~3.22 (1H, m, C^4-H), 3.79 (1H, ddd, J = 13.6, 10.8, 4.0 Hz, C^3-H), 3.91~3.99 (1H, m, C^3-H), 4.26 (2H, q, J = 7.1 Hz, $OC\underline{H}_2CH_3$), 5.50 (1H, s, C^1-H), 7.35 (1H, d, *J* = 8.4 Hz, C^5-H), 8.10 (1H, dd, *J* = 8.4, 2.4 Hz, C^6-H), 8.37 (1H, d, *J* = 2.4 Hz, C^8-H).

Substituent Effects on the Nitrogen Atom of β-Phenethylamines (Scheme 2).

Typical Procedure. $SnCl_4$ (2.4 mL, 20.5 mmol) was added to a solution of *N*-acetyl-β-phenethylamine (**7a**) (1.44 g, 8.8 mmol) and ethyl chloro(methylthio)acetate (**1**) (1.79 g, 10.6 mmol) in 1,2-dichloroethane (20 mL) at rt. The reaction mixture was refluxed for 40 min. After cooling, the reaction mixture was poured into ice-water and extracted with AcOEt. The AcOEt extract was washed with water, sat. *aq*.$NaHCO_3$, and sat. brine, dried over $MgSO_4$, and evaporated *in vacuo*. The oily residue was purified by column chromatography on SiO_2 with n-hexane - AcOEt (1 : 1, v/v) as eluant to give **9a** (1.76 g) in 67% yield.

9a: colorless oil. IR (neat) cm^{-1} : 3290, 1732, 1651; MS (APCI) *m/z*: 296 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.28 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.94 (3H, s, $COCH_3$), 2.10 (3H, s, SCH_3), 2.81 (2H, t, *J* = 7.0 Hz, $ArC\underline{H}_2CH_2N$), 3.50 (2H, q, *J* = 7.0 Hz, $ArCH_2C\underline{H}_2N$), 4.15~4.27 (2H, m, $OC\underline{H}_2CH_3$), 4.48 (1H, s, SCHCO), 5.57 (1H, br s, D_2O exchangeable), 7.16~7.19 (2H, m, Aromatic H), 7.39~7.69 (2H, m, Aromatic H).

9b: colorless oil, yield 66%. IR (neat) cm^{-1}: 3325, 1710; MS (FAB) *m/z*: 350 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.27 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 2.09 (3H, s, SCH_3), 2.88 (2H, t, *J* = 7.0 Hz, $ArC\underline{H}_2CH_2N$), 3.61 (2H, q, *J* = 7.0 Hz, $ArCH_2C\underline{H}_2N$), 4.16~4.26 (2H, m, $OC\underline{H}_2CH_3$), 4.48 (1H, s, $C\underline{H}SCH_3$), 6.34 (1H, br s, D_2O exchangeable), 7.16~7.19 (2H, m, Aromatic H), 7.42~7.46 (2H, m, Aromatic H).

Desulfonylation Reaction of 3a, d, e by DBU Treatment (Scheme 3).

Typical Procedure. Under argon atmosphere, DBU (392 mg, 2.6 mmol) was added to a stirred solution of **3e** (1.00 g, 2.6 mmol) in degassed toluene (20 mL) on an ice bath. The reaction mixture was stirred for 10 min at the same temperature and then poured into ice-water and extracted with AcOEt. The AcOEt extract was washed with water and sat. brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was separated by column chromatography on SiO_2 with AcOEt - n-hexane (1 : 1, v/v) as eluant to give **10e** (500 mg) in 79% yield and **11e** (30 mg) in 5% yield, respectively.

10a: colorless oil, yield 39%. IR (neat) cm^{-1}: 1726, 1619; MS (FAB) *m/z*: 204 $[M+H]^+$; High MS (FAB) *m/z*: Calcd for $C_{12}H_{14}NO_2$: 204.1025, Found: 204.1022; ^{1}H-NMR ($CDCl_3$) δ 1.42 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.74~2.79 (2H, m, C^4-H), 3.86~3.91 (2H, m, C^3-H), 4.43 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 7.18~7.22 (1H, m, C^5-H), 7.28~7.34 (1H, m, C^7-H), 7.40 (1H, dt, *J* = 7.5, 1.5 Hz, C^6-H), 7.69 (1H, dd, *J* = 7.5, 1.1 Hz, C^8-H). ^{13}C-NMR ($CDCl_3$) δ 14.24, 25.44, 47.72, 62.03, 126.29, 127.11, 127.29,

127.74, 131.82, 137.79, 159.96, 165.04.

11a: colorleess oil, yield 29%. IR (neat) cm^{-1}: 1721; MS (FAB) *m/z* : 202 $[M+H]^+$; High MS (FAB) *m/z*: Calcd for $C_{12}H_{12}NO_2$: 202.0868, Found: 202.0866 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.51 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 4.59 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 7.65~7.75 (2H, m, Aromatic H), 7.81 (1H, dd, *J* = 5.7, 0.7 Hz, C^4-H), 7.86~7.89 (1H, m, Aromatic H), 8.63 (1H, d, *J* = 5.7 Hz, C^3-H), 8.75~8.79 (1H, m, Aromatic H). ^{13}C-NMR ($CDCl_3$) δ: 14.39, 62.23, 124.21, 126.61, 126.95, 127.34, 128.88, 130.76, 137.15, 141.93, 149.27, 166.32.

10d: colorless oil, yield 32%. IR (neat) cm^{-1}: 1724, 1620; MS (FAB) *m/z*: 262 $[M+H]^+$; High MS (FAB) *m/z*: Calcd for $C_{14}H_{15}NO_4$: 262.1079. Found: 262.1071 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.45 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.81~2.86 (2H, m, C^4-H), 3.90~3.96 (2H, m, C^3-H), 3.93 (3H, s, CO_2Me), 4.47 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 7.30 (1H, d, *J* = 7.9 Hz, C^5-H), 8.09 (1H, dd, *J* = 7.9, 1.7 Hz, C^6-H), 8.39 (1H, d, *J* = 1.7 Hz, C^8-H). ^{13}C-NMR ($CDCl_3$) δ 14.23, 25.66, 47.46, 52.38, 62.29, 126.35, 127.99, 128.35, 129.56, 132.78, 142.92, 159.18, 164.59, 166.63.

11d: colorleess needles, mp 88~88.5°C (AcOEt - n-hexane), yield 37%. IR (nujol) cm^{-1}: 1715; MS (APCI) *m/z*: 260 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.54 (3H t, *J* =7.1 Hz, $OCH_2C\underline{H}_3$), 4.02 (3H, s, CO_2Me), 4.63 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 7.86 (1H, dd, *J* = 5.7, 0.9 Hz, C^4-H), 7.94 (1H, d, *J* = 8.6 Hz, C^5-H), 8.32 (1H, dd, *J* = 8.6, 1.7 Hz, C^6-H), 8.72 (1H, d, *J* = 5.7 Hz, C^3-H), 9.50~9.51 (1H, m, C^8-H); ^{13}C-NMR ($CDCl_3$) δ 14.37, 52.70, 62.55, 123.93, 126.18, 130.19, 130.38, 139.02, 143.86, 150.54, 165.83, 166.61. *Anal.* Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40, Found: C, 64.69; H, 5.01; N, 5.37.

10e: pale orange needles, mp 101~101.5°C (AcOEt - n-hexane). IR (nujol) cm^{-1}: 1717; MS (APCI) *m/z*; 249 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.46 (3H t, *J* =7.1 Hz, $OCH_2C\underline{H}_3$), 2.86~2.92 (2H, m, C^4-H), 3.97~4.02 (2H, m, C^3-H), 4.49 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 7.41 (1H, d, *J* = 8.4 Hz, C^5-H), 8.28 (1H, dd, *J* = 8.4, 2.4 Hz, C^6-H), 8.71 (1H, d, J = 2.4 Hz, C^8-H). ^{13}C-NMR ($CDCl_3$) δ: 14.22, 25.57, 47.38, 62.64, 122.54, 126.28, 126.89, 128.81, 145.03, 147.40, 157.67, 163.95. *Anal.* Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28, Found: C, 58.39; H, 4.81; N, 11.25.

11e: colorless solid. IR (nujol) cm^{-1}: 1709; MS (APCI) *m/z*: 247 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.55 (3H, t, *J* =7.1 Hz, $OCH_2C\underline{H}_3$), 4.65 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 7.95 (1H, dd, *J* = 5.5, 0.91 Hz, C^4-H), 8.07 (1H, d, *J* = 9.2 Hz, C^5-H), 8.52 (1H, dd, *J* = 9.2, 2.2 Hz, C^6-H), 8.85 (1H, d, *J* = 5.5 Hz, C^3-H), 9.86~9.87 (1H, m, C^8-H).

Acidic Hydrolysis of 3a, b, e to 12 a, b, e (Scheme 4).

Typical Procedure. A mixture of **3a** (1.76 g, 5.1 mmol), 6N-HCl (40 mL) and dioxane (40 mL) was refluxed for 4.5 h. After removal of solvent, the residue was extracted with AcOEt. The AcOEt extract was washed with water and sat. brine, dried over $MgSO_4$, filtered through charcoal and evaporated *in vacuo*. The crude product was recrystalized from EtOH to give **12a** (1.67 g) in 79% yield.

12a: colorless prisms, mp 197~199°C (decomp). IR (nujol) cm^{-1}: 1715; MS (ESI) *m/z*: 316 $[M-H]^-$; ^{1}H-NMR (DMSO-d_6) δ 2.63~2.73 (1H, m, C^4-H), 2.81 (1H, dt, J = 16.3, 4.8 Hz, C^4-H), 3.58~3.78 (2H, m, C^3-H), 5.41 (1H, s, C^1-H), 7.08~7.23 (3H, m, Aromatic H), 7.38~7.44 (1H, m, Aromatic H), 7.51~7.65 (3H, m, Aromatic H), 7.80~7.84 (2H, m, Aromatic H). *Anal.* Calcd for $C_{16}H_{15}NO_4S$: C, 60.55; H, 4.76; N, 4.41; S, 10.10. Found: C, 60.66; H, 4.73; N, 4.39; S, 10.08.

12b: colorless prisms, mp 196~196.5°C (decomp) (AcOEt - n-hexane), yield 84%. IR (nujol) cm^{-1}: 3060, 1715; MS (ESI) *m/z*: 334 $[M-H]^-$; ^{1}H-NMR (DMSO-d_6) δ 2.60 (1H, dt, J = 16.3, 8.1 Hz, C^4-H), 2.74 (1H, dt, J = 16.3, 4.6 Hz, C^4-H), 3.66 (2H, dd, J = 8.1, 4.6 Hz, C^3-H), 5.55 (1H, s, C^1-H), 7.05 (1H, dt, J = 8.6, 2.8 Hz, C^6-H), 7.13 (1H, dd, J = 8.6, 6.0 Hz, C^5-H), 7.27 (1H, dd, J = 9.9, 2.8 Hz, C^8-H), 7.50~7.65 (3H, m, Aromatic H), 7.80~7.84 (2H, m, Aromatic H), 13.28 (1H, s, CO_2H, D_2O exchangeable). *Anal.* Calcd for $C_{16}H_{14}NO_4FS$: C, 57.31; H, 4.21; N, 4.18; F, 5.67; S, 9.56. Found: C, 57.28; H, 4.06; N, 4.01; F, 5.76; S, 9.43.

12e: colorless powder, mp 172~173°C, yield 84%. IR (nujol) cm^{-1}: 1720; MS (ESI) *m/z*: 361 $[M-H]^-$; ^{1}H-NMR (DMSO-d_6) δ 2.70 (1H, ddd, J = 17.4, 10.3, 6.8 Hz, C^4-H), 2.88 (1H, dt, J = 17.4, 4.4 Hz, C^4-H), 3.63 (1H, ddd, J = 13.5, 10.3, 4.4 Hz, C^3-H), 3.76~3.84 (1H, m, C^3-H), 5.84 (1H, s, C^1-H), 7.37 (1H, d, J = 8.6 Hz, C^5-H), 7.48~7.63 (3H, m, Aromatic H), 7.82~7.86 (2H, m, Aromatic H), 8.04 (1H, dd, J = 8.6, 2.4 Hz, C^6-H), 8.38 (1H, dd, J = 2.4 Hz, C^8-H), 13.58 (1H, s, CO_2H, D_2O exchangeable). *Anal.* Calcd for $C_{16}H_{14}N_2O_6S$: C, 53.03; H, 3.89; N, 7.73; S, 8.85. Found: C, 52.93; H, 3.85; N, 7.54; S, 8.74.

Synthesis of 3,4-Dihydroisoquinolines (13 a~c) from *N*, *N*-Dimethylsulfamoyl Derivatives (6a~c) by Acidic Hydrolysis (Scheme 5).

Typical Procedure. A mixture of **6a** (4.02 g, 12.9 mmol) and 6N-HCl (40 mL) was refluxed overnight. After removal of solvent, the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with sat. *aq.* $NaHCO_3$ and sat. brine, dried over $MgSO_4$ and evaporated *in vacuo*. The crude residue was purified by

column chromatography on SiO_2 with $CHCl_3$ as an eluant to give **13a** (1.30 g) in 77% yield.

13a: colorless oil. IR (neat) cm^{-1}: 1625; MS (GC-EI) *m/z*: 131 $[M]^+$; ^{1}H-NMR ($CDCl_3$) δ 2.73~2.78 (2H, m, C^4-H), 3.75~3.81 (2H, m, C^3-H), 7.15~7.17 (1H, m, Aromatic H), 7.25~7.39 (3H, m, Aromatic H), 8.34 (1H, s, C^1-H).

13b: crude amber solid, mp 47~50°C, yield 79%. IR (nujol) cm^{-1}: 1615; MS (GC-EI) *m/z*: 149 $[M]^+$. ^{1}H-NMR ($CDCl_3$) δ 2.69~2.74 (2H, m, C^4-H), 3.75~3.81 (2H, m, C^3-H), 6.99 (1H, dd, J = 8.4, 2.6 Hz, C^8-H), 7.06 (1H, dt, J = 8.2, 2.6 Hz, C^6-H), 7.13 (1H, dd, J = 8.2, 5.3 Hz, C^5-H), 8.30 (1H, s, C^1-H).

13c: crude amber solid, mp 91.5~92.5°C, yield 70%. IR (nujol) cm^{-1}: 1590; MS (APCI) *m/z*: 177$[M+H]^+$; ^{1}H-NMR ($CDCl_3$) δ 2.85~2.90 (2H, m, C^4-H), 3.84~3.90 (2H, m, C^3-H), 7.36 (1H, d, J = 8.2 Hz, C^5-H), 8.15 (1H, d, J = 2.2 Hz, C^8-H), 8.24 (1H, dd, J = 8.2, 2.4 Hz, C^6-H), 8.44 (1H, s, C^1-H).

Synthesis of 1-Ethoxycarbonyl-7-fluoroisoquinoline (11b) from *N,N*-Dimethylsulfamoyl Derivatives (6b) by DBU Treatment (Scheme 5).

Under argon atmosphere, DBU (970 mg, 6.4 mmol) was added to a stirred solution of **6b** (1.00 g, 3.0 mmol) in 20 mL of degassed toluene at rt. The mixture was stirred at rt for 17 h and poured into water and extracted with AcOEt. The AcOEt extract was washed with water and sat. brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was separated by column chromatography on SiO_2 with AcOEt - n-hexane (1 : 2, v/v) as eluant to afford **11b** (400 mg, 60%) and **6b** (290 mg, 29%), respectively.

11b: colorless needles, mp 70.5~71.5°C (Et_2O - n-hexane). IR (nujol) cm^{-1}: 1704; MS (APCI) m/z: 220 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$) δ 1.52 (3H, t, J =7.1 Hz, $OCH_2C\underline{H}_3$), 4.59 (2H, q, J = 7.1 Hz, $OC\underline{H}_2CH_3$), 7.53 (1H, ddd, J = 9.2, 8.1, 2.6 Hz, C^6-H), 7.83 (1H, dd, J = 5.5, 0.7 Hz, C^4-H), 7.90 (1H, dd, J = 9.2, 5.5 Hz, C^5-H), 8.55~8.59 (1H, m, C^8-H), 8.64 (1H, d, J = 5.5 Hz, C^3-H). ^{13}C-NMR ($CDCl_3$) δ: 14.38, 62.37, 110.53 (d, J = 23.8 Hz), 121.70 (d, J = 26.1 Hz), 124.20 (d, J = 1.7 Hz), 128.06 (d, J = 9.7 Hz), 130.04 (d, J = 8.9 Hz), 134.38 (d, J = 0.9 Hz), 141.52 (d, J = 2.6 Hz), 148.00 (d, J = 6.3 Hz), 162.05 (d, J = 250.8 Hz), 165.97. *Anal.* Calcd for $C_{12}H_{10}NO_2F$: C, 65.75; H, 4.60; N, 6.39, F, 8.67, Found: C, 65.64; H, 4.50; N, 6.30; F, 8.47.

Cyclization Reaction of Methylthio Derivative (4g) to Tetrahydroisoquinoline (3g) by $SnCl_4$ (Scheme 7).

$SnCl_4$ (1.3 mL, 11.1 mmol) was added to a solution of **4g** (4.73 g, 10.4 mmol) in 1,2-dichloroethane (40 mL) on an ice bath. The mixture was stirred at rt for 30 min and then at reflux temperature for 30 min. After cooling, the reaction mixture was poured into ice - water and extracted with AcOEt. The AcOEt extract was washed with water, sat. *aq*.$NaHCO_3$, and sat. brine, dried over $MgSO_4$, and evaporated *in vacuo*. The oily residue was purified by column chromatography on SiO_2 with n-hexane : AcOEt (5 : 3, v/v) as eluant to give **3g** (2.87 g) in 68% yield, whose spectral data (mp, IR, ^{1}H-NMR) were identical with the authentic sample described in general procedure (Table 1 and Scheme 1).

Et_3SiH Reduction of *N*-Benzenesulfonamide-β-phenethylamine (2e) under Cyclization Condition (Scheme 8).

$SnCl_4$ (0.88 mL, 7.5 mmol) was added to a stirred solution of **1** (1.26 g, 7.5 mmol) and **2e** (1.00 g, 3.3 mmol) in dichloroethane (20 mL) at rt. After 10min, Et_3SiH (1.30 mL, 8.1 mmol) was added to the mixture, and the whole was stirred at the same temperature for 1 h. The mixture was diluted with H_2O and AcOEt. The organic layer was washed with sat. $NaHCO_3$ and sat. brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was separated by column chromatography on SiO_2 with n-hexane : AcOEt (7:3, v/v) as eluant to give the reductive alkylation product (**16**) (0.85 g) in 66% yield and the starting material (**2e**) (0.15 g) recovered in 15% yield.

16: colorless lieflets, mp 90~91°C (AcOEt - n-hexane). IR (nujol) cm^{-1}: 1746; MS (APCI) *m/z*:393 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$) δ 1.18 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 3.04 (2H, dd, *J* = 7.9, 7.3 Hz, $ArC\underline{H}_2CH_2N$), 3.53 (2H, dd, *J* = 7.9, 7.3 Hz, $ArCH_2C\underline{H}_2N$), 4.00 (2H, s, NCH_2CO), 4.06 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 7.32~7.37 (2H, m, Aromatic H), 7.46~7.53 (2H, m, Aromatic H), 7.56~7.61 (1H, m, Aromatic H), 8.12~8.13 (2H, m, Aromatic H), 8.15~8.16 (2H, m, Aromatic H). *Anal.* Calcd for $C_{18}H_{20}N_2O_6S$: C, 55.09; H, 5.14; N, 7.14, S, 8.17, Found: C, 54.88; H, 5.07; N, 7.05; S, 8.14.

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12. Et_3SiH reduction of *N*-acyl-β-phenethylamines (**7a, b**) under the cyclization condition (Scheme 8) only recovered the starting material (**7a, b**) in 81 and 92% yields, respectively. In the crude mixture, no reductive alkylation product (**17**) was detected by ^{1}H-NMR spectrum.

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