A NOVEL CYCLIZATION OF ELECTRON DEFICIENT *N*-BENZENESULFONYL-β-PHENETHYLAMINES USING ETHYL CHLORO(METHYLTHIO)ACETATE. SYNTHESIS OF ETHYL 1,2,3,4-TETRAHYDROISOQUINOLINE-1-CARBOXYLATES

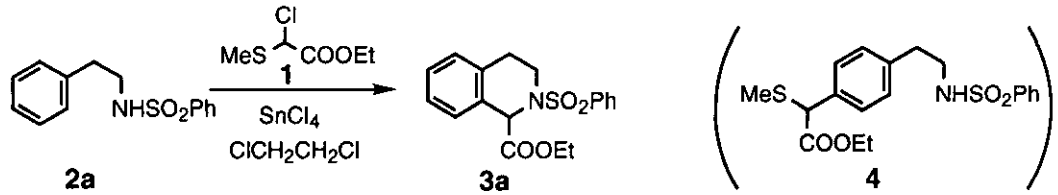
Harumichi Kohno and Yasuo Sekine*

Lead Optimization Research Laboratory, Tanabe Seiyaku Co., Ltd.

2-2-50 Kawagishi, Toda, Saitama 335, Japan

Abstract -The reaction of electron deficient *N*-benzenesufonyl-β-phenethylamines (**2**) with ethyl chloro(methylthio)acetate (**1**) gave ethyl 2-benzenesulfonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylates (**3**) in high yields. We examined the effects of a substituent on the benzene ring and several Lewis acids in this cyclization.

Ethyl chloro(methylthio)acetate (**1**) is a useful Friedel-Crafts alkylating agent developed by Tamura *et al.*[1] This reagent has advantage that the second alkylation does not occur on the benezene ring.[1a] In the course of the synthesis of phenylacetic acid derivatives, we found that the treatment of *N*-benzenesulfonyl-β-phenethylamine (**2a**) with ethyl chloro(methythio)acetate (**1**) afforded ethyl 2-benzenesulfonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (**3a**) in 48% yield in the presence of $SnCl_4$ at room temperature and the starting material (**2a**) was recovered in 50% yield (Scheme I). Surprisingly, no Friedel-Crafts product (**4**) was detected in this reaction.

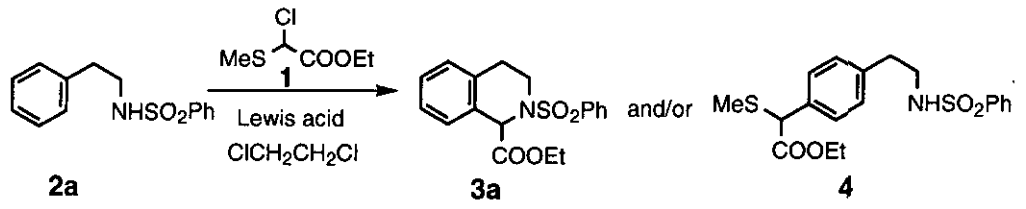


2a **3a** **4**

Scheme I

Pictet-Spengler synthesis[2] is one of the fundamental reaction for the preparation of 1,2,3,4-tetrahydroisoquinoline derivatives. This cyclization occurs only when the ring-closure position is activated by electron donating substituents. There are some modified methods to increase the electrophilicity of iminium intermediate introducing an electron withdrawing substituent, such as acyl[3-5] and sulfonyl[5-7] group, on the nitrogen. However, 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. We report here a novel cyclization of electron deficient *N*-benzenesulfonyl-β-phenethylamines with ethyl chloro(methylthio)-acetate **1** to ethyl 2-benzenesulfonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylates.

In order to optimize the reaction conditions, we examined several Lewis acids (Scheme II). The results are summarized in Table I. In the case of $AlCl_3$ in 1,2-dichloroethane at room temperature, *N*-benzenesulfonyl-β-phenethylamine (**2a**) gave the Friedel-Crafts product (**4**) in 80% yield (run 1). In this reaction, the cyclized product (**3a**) was not detected. $TiCl_4$ gave the cyclized product (**3a**) in 57~63% yield along with the Friedel-Crafts product (**4**) in 4~7% yield (runs 2, 3). When a weaker Lewis acid such as $SnCl_4$, $BF_3{\cdot}OEt_2$ and $ZnCl_2$ was employed, the Pictet-Spengler like cyclization proceeded without affording the Friedel-Crafts product (**4**) (runs 4~6). These results indicate that $SnCl_4$ is the most suitable Lewis acid in this cyclization.



Scheme II

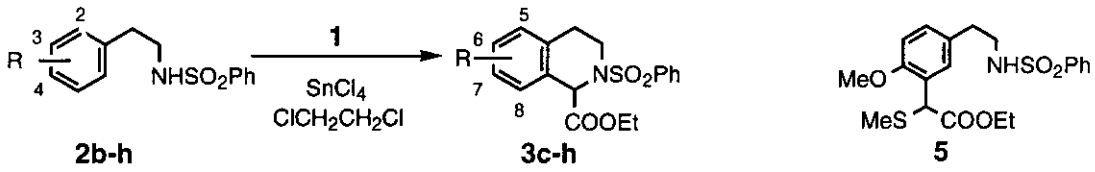
Table I Effects of Lewis acids[a]

run	Lewis acid	Temp.	Time / h	Product (yield %)[b]
1	$AlCl_3$	room temperature	3	**4** (80)
2	$TiCl_4$	room temperature	3	**3 a** (57) **4** (7) **2 a** (37)
3	$TiCl_4$	reflux	1.5	**3 a** (63) **4** (4) **2 a** (34)
4	$SnCl_4$	reflux	1.5	**3 a** (91)
5	BF_3-OEt_2	reflux	3	**3 a** (70) **2 a** (30)
6	$ZnCl_2$	reflux	3	**3 a** (75) **2 a** (25)

a) The reaction was carried out by using 1.2 eq. of **1** and 2.2 eq. of Lewis acid in 1,2-dichloroethane.

b) All compounds gave the satisfactory spectral data.

We next examined the effects of substituents on the benzene ring (Scheme III). The results are summarized in Table II. Phenethylamine derivative bearing a methoxy group on the benzene ring **2b** gave the only Friedel-Crafts product (**5**) in a quantitative yield (run 1). However, when an electron withdrawing substituent is on the benzene ring **2c-h**, the cyclization proceeded in high yields (runs 2-7). Even a nitro group did not prevent the cyclization (run 7). In the case of carbonyl compound (**2g**), the cyclized product (**3g**) was obtained in only 44% yield (run 6).



2b-h **3c-h** **5**

Scheme III

Table II Effects of substituents on the phenyl group[a]

run	R in **2**[b]		Temp.	Time / h	Product (yield %)[b]	
1	4-MeO	**2b**	room temperature	1.5	**5** (quant.)	
2	3-Cl	**2c**	reflux	1.5	**3c** (74)[c]	**2c** (18)
3	4-Cl	**2d**	reflux	3.0	**3d** 7-Cl (80)	**2d** (20)
4	3-F	**2e**	reflux	1.5	**3e** (85)[d]	**2e** (12)
5	4-F	**2f**	reflux	1.5	**3f** 7-F (78)	**2f** (22)
6	4-COMe	**2g**	reflux	3.0	**3g** 7-COMe (44)	**2g** (22)
7	4-NO_2	**2h**	reflux	1.5	**3h** 7-NO_2 (91)[e]	

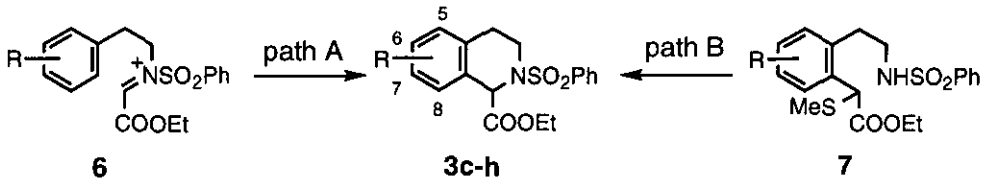
a) The reaction was carried out by using 1.2 eq. of **1** and 2.2 eq. of $SnCl_4$ in 1,2-dichloroethane.

b) All compounds gave the satisfactory spectral data. c) The ratio of 6-Cl and 8-Cl is 87 : 13, determined by ^{1}H-nmr.

d) The ratio of 6-F and 8-F is 94 : 6, determined by ^{1}H-nmr. e) 2.3eq. of **1** and 2.2eq. of $SnCl_4$ were used.

Two possible pathways of the cyclization reaction are illustrated in Scheme IV. The cyclization proceeds predominantly when a weaker Lewis acid is employed (runs 2~6 in Table I) and an electron withdrawing substituent is on the phenyl moiety (runs 2~7 in Table II). This cyclization depends upon the electron density of the benzene ring and the activity of Lewis acid. Furthermore, the cyclization is not affected by the position of halogen (runs 2, 3 and runs 4, 5 in Table II). These results suggest that the alkylation reaction on the nitrogen of *N*-benzenesufonyl-β-phenethyamine derivatives (**2**) may occur first and then be followed by the

cyclization reaction (pathA). Iminium cation (**6**) is supposed to be an intermediate of this cyclization reaction, but the mechanism is not clear now.



6 **3c-h** **7**

Scheme IV

A typical procedure for cyclization of **2h** is as follows : $SnCl_4$ (0.75 ml, 6.5 mmol) was added to a solution of **2h** (0.92 g, 3.0 mmol) and ethyl chloro(methylthio)acetate (**1**) (1.12 g, 6.7 mmol) in 1,2-dichloroethane (10 ml) at room temperature. The reaction mixture was refluxed for 1.5 h. After cooling to room temperature, the reaction mixture was poured into ice-water and extracted with AcOEt. The extract was washed with water, sat. $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The resulting oily residue was purified by column chromatography on SiO_2 with n-hexane:AcOEt (7:3) as a solvent to give 1.06 g of **3h**[8] as colorless prisms in 91% yield, mp 87.5-88.0°C.

REFERENCES

1. a) Y. Tamura, H. D. Choi, H. Shindo, and H. Ishibashi, *Chem. Pharm. Bull.*, 1982, **30**, 915.
   b) Y. Tamura, H. D. Choi, M. Mizutani, Y. Ueda, and H. Ishibashi, *ibid.*, 1982, **30** 3574.
   c) H. Ishibashi, M. Ikeda, H. D. Choi, H. Nakagawa, Y. Ueda, and Y. Tamura, *ibid.*, 1985, **33**, 5310.
2. W. M. Whaley and T. R. Govindachari, *Org. React.*, 1951, **6**, 151.
3. R. R. Wittekind and S. Lazarus, *J. Heterocycl. Chem.*, 1971, **8**, 495.
4. N. M. Mollov and A. P. Venkov, *Synthesis*, 1978, 62.
5. A. P. Venkov and L. K. Lukanov, *Synthesis*, 1989, 59.
6. O. O. Orazi, R. A. Corral, and H. Giaccio, *J. Chem. Soc., Perkin Trans. I*, 1986, 1977.
7. J. Zinczuk, I. H. Sorokin, O. O. Orazi, and R. A. Corral, *J. Heterocycl. Chem.*, 1992, **29**, 859.
8. The spectral data of **3h** are shown. ^{1}H-nmr (300 MHz, $CDCl_3$) δ 1.19 (t, J=7.16 Hz, 3H), 2.88~3.09 (m, 2H), 3.73~4.11 (m, 4H), 5.76 (s, 1H), 7.30 (d, J=8.54 Hz, 1H), 7.83~7.87 (m, 2H), 7.48~7.61 (m, 3H), 8.08 (dd, J=8.54, 2.20 Hz, 1H), 8.33 (d, J=2.20 Hz, 1H); ir (neat) cm^{-1}, 1740 (C=O); ms (FAB) m/z, 391 (MH^+).

Received, 29th March, 1995