Practical Synthesis of Optically Active Fluorine-substituted α-Phenylethylamines by Retardation of Hydrogenolytic Cleavage at Benzylic Position

Masatomi Kanai,* Manabu Yasumoto, Yokusu Kuriyama, Kenjin Inomiya, Yutaka Katsuhara, Kimio Higashiyama,† and Akihiro Ishii*

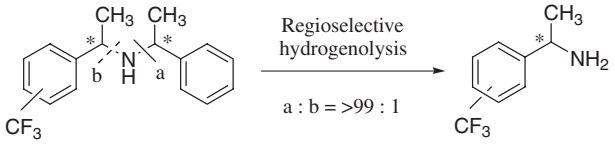
Chemical Research Center, Central Glass Co., Ltd., Kawagoe 350-1151

†*Faculty of Pharmaceutical Science, Hoshi University, Shinagawa, Tokyo 142-8501*

(Received July 29, 2004; CL-040897)

High regioselectivity in hydrogenolysis of bis(α-methylbenzyl)amines having a fluorine atom on aromatic ring results from retardation of hydrogenolytic cleavage at benzylic position of fluorine-substituted aromatic ring.

Recently we reported that highly regioselective hydrogenolysis of bis(α-methylbenzyl)amines proceeded under influence of trifluoromethyl group on aromatic ring. (Scheme 1).[1] This regioselectivity was governed not by electronic effect but by steric effect of trifluoromethyl group.



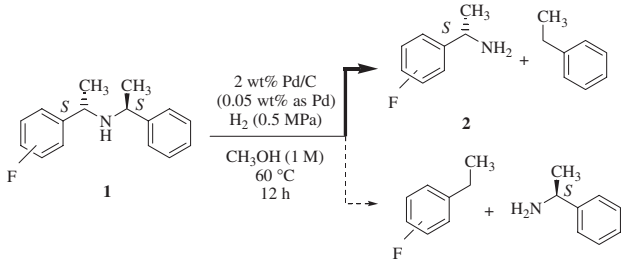
Scheme 1. Regioselective hydrogenolysis of bis(α-methylbenzyl)amines affected by trifluoromethyl group.

In synthetic application for optically active fluorine-substituted α-phenylethylamines,[2–4] we were interested in regioselective hydrogenolysis of bis(α-methylbenzyl)amines affected by fluorine substituent.[5] In this communication, we disclose that a fluorine atom at any position of aromatic ring plays an important role to give a high regioselectivity of >99:1, and this high regioselectivity results from retardation of hydrogenolytic cleavage at the benzylic position.

Diastereomerically pure bis(α-methylbenzyl)amines (**1**) having fluorine substituent at *o*-, *m*-, *p*-, and 3,5-di-position were prepared by a similar method as described in previous reports.[1,5,6] First, we examined regioselective hydrogenolysis using free base of **1** (Table 1, Entries 1–4). Surprisingly, we found that even at any fluorine substituted position high regioselectivities of >99:1 were observed under optimized reaction conditions;[1] 2 wt % Pd/C (0.05 wt % as Pd),[7] H_2 0.5 MPa, CH_3OH (1 M), 60 °C, 12 h. However, reaction rates were slow in all cases, especially for *p*-F-**1**. They were dramatically increased using organic acid salts of **1** without any decrease of regioselectivity (Entries 5–8).

This high regioselectivity might be governed mainly by steric effect of fluorine atom in a similar manner of trifluoromethyl group.[1] However, this consideration was not easily acceptable, because fluorine atom would most closely resemble and mimic hydrogen atom with respect to steric requirement.[8] In fact, in competitive hydrogenolytic cleavage of 4-fluoro-4′-methyl- and 4-fluoro-4′-ethyl-disubstituted substrates (**3** and **4**)[9] under the same reaction conditions,[10] expected regioselectivities governed by steric effect of substituents were not observed (Figure 1). Clearly methyl and ethyl groups were sterically more hindered than fluorine atom. Therefore, high regioselectivity in hydrogenolysis of fluorine-substituted **1** could not be rationalized only by the steric effect of fluorine atom.

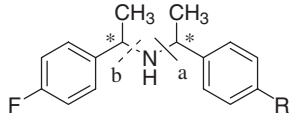
Table 1. Regioselective hydrogenolysis of bis(α-methylbenzyl)amines (**1**) affected by fluorine substituent[a]



Entry	Substrate (**1**)	Conversion[b]	Regioselectivity[c]
1	*o*-F	33%	>99:1
2	*m*-F	39%	>99:1
3	*p*-F	5%	>99:1
4	3,5-di-F	61%	>99:1
5	*o*-F (phthalic acid salt)	99%	>99:1
6	*m*-F (phthalic acid salt)	99%	>99:1
7	*p*-F[d]	99%	>99:1
8	3,5-di-F[d]	99%	>99:1

[a]Regioselective hydrogenolysis was carried out on a 10 mmol scale.
[b]Conversion was determined by GC analysis.
[c]Regioselectivity was determined by the ratio of ethylbenzene vs fluorine-substituted ethylbenzene in GC analysis.
[d]Acetic acid (5.0 equiv.) was added.

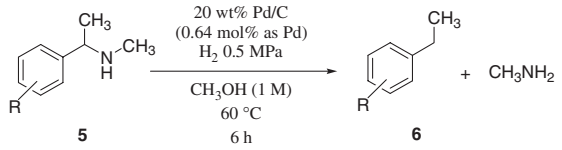
The hydrogenolytic reaction rate affected by various substituents was examined using *N*-methyl secondary amines **5** as a model substrate (Table 2). Results of Entries 1–4 seemed to show the order of steric size. On the other hand, the reaction rate was extremely retarded by incorporating a fluorine atom on the



3: R = CH_3, a : b = >99 : 1, conversion 35%
4: R = C_2H_5, a : b = 84 : 16, conversion 9%

Figure 1. Competitive hydrogenolytic cleavage of 4-fluoro-4′-methyl- and 4-fluoro-4′-ethyl-disubstituted substrates (**3** and **4**).

Table 2. Hydrogenolytic reaction rate of *N*-methyl secondary amines (**5**) affected by various substituents[a]



5 **6**

Entry	Substrate (**5**) (R=)	Conversion[b]	Relative Reaction Rate
1	*p*-H	77%	1
2	*p*-CH_3	60%	0.78
3	*p*-C_2H_5	49%	0.64
4	*p*-CF_3	42%	0.55
5	*p*-F	9%	0.12
6	*m*-F	7%	0.09
7	3,5-di-F	0.2%	<0.01

[a]Regioselective hydrogenolysis was carried out on a 2 mmol scale.
[b]Conversion was determined by GC analysis.

aromatic ring (Entries 5–7). These results could rationalize high regioselectivities observed in Table 1 and unexpected regioselectivities shown in Figure 1. The hydrogenolytic cleavage rate at the benzylic position having a fluorine atom on the aromatic ring was even slower than that at the benzylic position of unsubstituted benzene ring.

Finally, practical synthesis of optically active fluorine-substituted α-phenylethylamines (**2**) was examined on a 100 gram scale.[11] Above-mentioned *o*-, *m*-, *p*-, and 3,5-di-F-**2** were obtained in total yields of 40–60% and enantiomeric excesses of >99.5% in all cases.

In conclusion, we found that high regioselectivity in hydrogenolysis of bis(α-methylbenzyl)amines having a fluorine atom on the aromatic ring resulted from retardation of hydrogenolytic cleavage at the benzylic position of fluorine-substituted aromatic ring, and could be applied to practical synthesis of optically active α-phenylethylamines having a fluorine atom at any position on the aromatic ring.

We thank Prof. Kenji Uneyama (Okayama University) for fruitful discussions.

References and Notes

1 M. Kanai, M. Yasumoto, Y. Kuriyama, K. Inomiya, Y. Katsuhara, K. Higashiyama, and A. Ishii, *Org. Lett.*, **5**, 1007 (2003).
2 Regioselective hydrogenolysis of bis(α-methylbenzyl)amines having electron-donating groups has been already reported. a) G. Bringmann, J.-P. Geisler, T. Geuder, G. Kunkel, and L. Kinzinger, *Liebigs Ann. Chem.*, **1990**, 795. b) G. Bringmann and J.-P. Geisler, *Tetrahedron Lett.*, **30**, 317 (1989).
3 Optically active fluorine-substituted α-phenylethylamines have been regarded as important intermediates in development of medicines. a) H. Kurata, T. Kohama, K. Kono, and K. Kitayama, WO 02051396 (2002). b) A. G. Taveras, C. J. Aki, R. W. Bond, J. Chao, M. Dwyer, J. A. Ferreia, J. Chao, Y. Yu, J. J. Baldwin, B. Kaiser, G. Li, J. R. Merritt, K. H. Nelson, and L. L. Rokosz, WO 0208364 (2002). c) B. A. Mckittrick, G. Guo, Z. Zhu, and Y. Ye, WO 02051808 (2002).
4 Recently enantioselective reductions of enamide have been reported. a) M. J. Burk, Y. M. Wang, and J. R. Lee, *J. Am. Chem. Soc.*, **118**, 5142 (1996). b) F.-Y. Zhang, C.-C. Pai, and A. S. C. Chan, *J. Am. Chem. Soc.*, **120**, 5808 (1998). c) W. Hu, M. Yan, C.-P. Lau, S. M. Yang, and A. S. C. Chen, *Tetrahedron Lett.*, **40**, 973 (1999). d) Y.-Y. Yang and T. V. RajanBabu, *Org. Lett.*, **2**, 4137 (2000).
5 Only regioselective hydrogenolysis of *ortho*-fluorine-substituted bis(α-methylbenzyl)amine has been reported to give a moderate regioselectivity of 89:11. However, its scope and limitation and effect of fluorine atom were not discussed at all. G. Bringmann and J.-P. Geisler, *J. Fluorine Chem.*, **49**, 67 (1990).
6 Diastereomeric mixtures of **1** were prepared through dehydration between corresponding fluorine-substituted acetophenones (100 mmol) and commercially available (*S*)-α-phenylethylamine (110 mmol), followed by reduction of resulting imines. Dehydration was performed in the presence of a catalytic amount of zinc chloride (1.00 mmol) in toluene (1 M) under reflux (15 h) with removal of produced water using a Dean–Stark trap in quantitative yields. Three *m*-, *p*-, and 3,5-di-F-imines were obtained solely as (*E*)-isomers, while *o*-F-imine contained a small amount of (*Z*)-isomer (*E*:*Z* = 85:15). Reduction was performed using sodium borohydride (100 mmol) in methanol (1 M) at 0 °C (7 h) in quantitative yields with moderate diastereomeric excesses [ca. 60–70% de (*S*,*S*) for *m*-, *p*-, and 3,5-di-F-**1**], except for *o*-F-**1** [20% de (*S*,*S*)]. Diastereomeric excesses of all bis(α-methylbenzyl)amines were easily improved to >99.5% (*S*,*S*) by recrystallization of phthalic acid salts in ca. 70% recovery yields.
7 Pd/C (NX-type, 5 wt %, water content 50 wt %, N. E. CHEMCAT) was used.
8 R. Filler, in "Organofluorine Chemicals and Their Industrial Applications," ed. by R. E. Banks, Ellis Horwood, Ltd., Chichester, UK (1979), Chap. 6.
9 Diastereomeric excesses of 4-fluoro-4′-methyl- and 4-fluoro-4′-ethyl-disubstituted substrates (**3** and **4**) were 67% (*S*,*S*) and 66% (*S*,*S*), respectively.
10 Acetic acid (5.0 equiv.) was added.
11 Typical procedure for (*S*)-*p*-F-**2**. (A) A solution containing 138 g (1.00 mol) of *p*-fluoroacetophenone, 133 g (1.10 mol) of (*S*)-α-phenylethylamine, and 1.36 g (0.01 mol) of $ZnCl_2$ in 500 mL of toluene was refluxed with azeotropic removal of water for 15 h using a Dean-Stark trap. Reaction mixture was washed with 1 M NaOH, a saturated aqueous solution of NH_4Cl (three times) to remove residual (*S*)-α-phenylethylamine, and brine. After removal of solvent under a reduced pressure, 241 g of *p*-F-imine was obtained in a quantitative yield. (B) Sodium borohydride (37.8 g, 1.00 mol) was added to a solution containing 241 g of *p*-F-imine in 1.00 L of methanol at <10 °C, and solution was stirred for at 0 °C (12 h). Reaction mixture was acidified with 1 M HCl and neutralized with 3 M NaOH. Extracted toluene solution was washed with brine. After removal of solvent under a reduced pressure, a diastereomeric mixture of *p*-F-**1** was obtained in a quantitative yield [243 g, 60% de (*S*,*S*)]. (C) To a solution containing 243 g (1.00 mol) of *p*-F-**1** in 360 mL of propan-2-ol and 500 mL of heptane, 166 g (1.00 mol) of phthalic acid was added and reaction mixture was heated until solid was dissolved. After temperature was lowered slowly to 20 °C, 229 g of phthalic acid salt of *p*-F-**1** was obtained by filtration in 70% recovery yield [99.5% de (*S*,*S*)]. (D) Phthalic acid salt of *p*-F-**1** was neutralized with 3 M NaOH. Extracted toluene solution was washed with brine. After removal of solvent under a reduced pressure, 136 g (0.56 mol) of obtained free base *p*-F-**1** in 600 mL of methanol was hydrogenolyzed in the presence of 2.72 g of Pd/C (0.05 wt % as Pd) under 0.5 MPa of H_2 pressure at 60 °C for 12 h. Pd catalyst was filtered off through a Celite pad, and after removal of solvent under a reduced pressure, residue was distilled (69 °C/7 mmHg) to give 76.4 g (0.55 mol) of *p*-F-**2** in 98% yield [GC purity = 99.9%, 99.7% ee, (*S*)].

Published on the web (Advance View) October 2, 2004; DOI 10.1246/cl.2004.1424