Pergamon

Tetrahedron Letters, Vol. 37, No. 52, pp. 9317-9320, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02211-3

A Facile Synthesis of (*S*)-(−)-7,8-Difluoro-3,4-dihydro-3-methyl-2*H*-1,4-benzoxazine by Zinc Chloride Assisted Mitsunobu Cyclization Reaction

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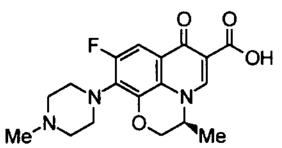
Abstract: A convenient procedure for preparation of the title compound of ≥99% ee starting from 1-(2,3-difluoro-6-nitrophenoxy)-2-propanone (**3**) is presented. The key reaction is the intramolecular cyclization reaction in the presence of zinc chloride. Copyright © 1996 Elsevier Science Ltd

(*S*)-(−)-7,8-Difluoro-3,4-dihydro-3-methyl-2*H*-1,4-benzoxazine (**2**) is a valuable precursor for the synthesis of levofloxacin (**1**),[1] a potent third generation quinolone antibacterial agent on the market. Several procedures[2] for preparation of this intermediate have been reported but these processes suffer from low yield, low optical purity, or difficulties with scale up. Our interest in development of new quinolones led us to examine routes to the key intermediate **2** from (*R*)-(−)-1-(6-amino-2,3-difluorophenoxy)-2-propanol (**7**).



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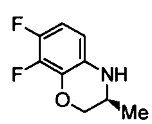
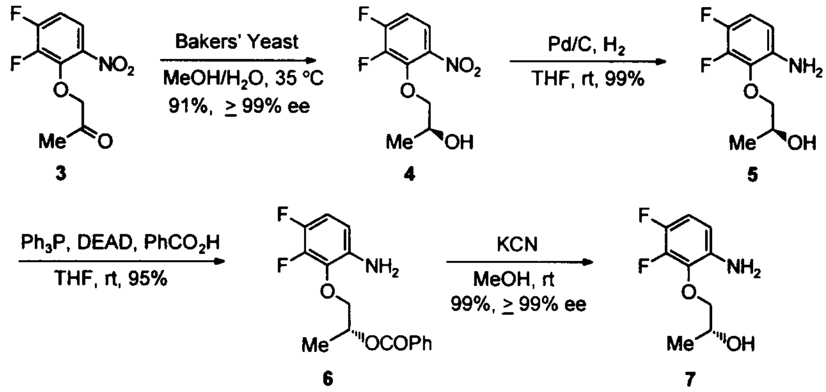


2

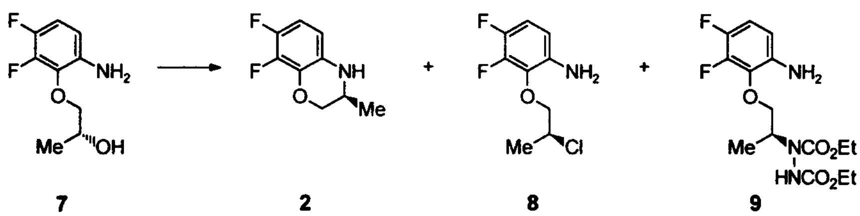
In this paper we describe an efficient, highly enantioselective procedure for preparation of **7**, together with new, mild and selective conditions for the primary aromatic amine *via* cyclization reaction to form the C-N bond. The compound **7** was prepared as shown in Scheme 1. Treatment of compound **3**[3] with Bakers' Yeast[4] in MeOH/H_2O at 35 °C for 6 hr afforded **4**[5] in 91% yield in ≥99% ee.[6] Reduction of **4** with 10% palladium on activated carbon under atmospheric pressure of H_2 in THF at RT for 4 hr to give **5** in quantitative yield, which was transformed into **6** by Mitsunobu inversion reaction[7] using Ph_3P, diethyl azodicarboxylate (DEAD), and benzoic acid in THF at RT for 1 hr in 95% yield. The mild hydrolysis of **6** with potassium cyanide in MeOH at RT for 1 day according to the literature[8] produced **7** in quantitative yield showing ≥99% ee.[9] The reaction of **7** under Mitsunobu reaction conditions in benzene did not generate the desired benzoxazine compound **2**, only to produce the DEAD adduct **9**[7b] as a major.



Scheme 1

When the reaction was performed in MeCN at reflux for 1 hr, the desired product **2** was observed in 18% by GC yield accompanied with a large amount of **9** in the reaction mixture. Encouraged by this result, $ZnCl_2$ was added to modify the reaction conditions. Use of anhydrous $ZnCl_2$ seemed to be an appropriate choice since there is a correlation in yield improvement with increasing amounts of $ZnCl_2$.

Table 1. Reactions of **7** under Ph_3P, DEAD, and $ZnCl_2$



Entry	Ph_3P/DEAD/$ZnCl_2$			Conditions (Δ, 1 hr)	Ratio[a] 2	8	9
1	3	3	0	benzene	-	-	major
2	3	3	0	MeCN	18	-	82
3	3	3	0.2	"	12	38	50
4	3	3	1	"	11	89	-
5	3	3	1.5	"	21	79	-
6	3	3	3	"	78(64)[b](≥99)[c]	22	-
7	3	3	4	"	94(76) (≥99)	6	-
8	3	3	5	"	95(75) (≥99)	5	-
9	3	3	10	"	95(50) (≥99)	5	-
10	1.1	1.2	3	"	61(36) (≥99)	3	36 (SM **7**)

[a] a ratio of the product mixture by capillary GC.
[b] an isolated yield.
[c] an enantiomeric excess by capillary GC.[11]

As shown in Table 1, the amount of $ZnCl_2$ is an important variable in this cyclization. The maximum yield was acquired when 400 M% of $ZnCl_2$ was employed and further addition of $ZnCl_2$ decreased the yield. Thus treatment of **7** with 300 M% of Ph_3P, 300 M% of DEAD, and 400 M% of $ZnCl_2$ in MeCN at reflux for 1 hr provided **2**[10] in 76% yield in ≥99% ee.[11] As of today, this is the first report to our knowledge on the intramolecular cyclization reaction for the primary aromatic amine under Mitsunobu reaction conditions to form the C-N bond.[7] Reactions using a various of metal halides were attempted but all has been inferior to the result with $ZnCl_2$. This important potential application of $ZnCl_2$ prompted us to examine the alternate reaction conditions in the hope of achieving a better and practical synthesis of **2**. Heating with Ph_3P and CCl_4 in MeCN has been known one of mild reaction conditions for chlorination of the hydroxy compound.[7c] When **7** was reacted with Ph_3P and CCl_4 in the presence of $ZnCl_2$, a similar effect of $ZnCl_2$ was detected as shown in Table 2. Reaction of **7** with 200 M% of Ph_3P, 400 M% of CCl_4, and 300 M% of $ZnCl_2$ in MeCN at reflux for 10 min resulted in formation of **2** in 52% yield in ≥99% ee. It is noteworthy that the enantiomerically pure benzoxazine compound **2** is easily synthesized within 10 min under mild reaction conditions from the readily available starting material in moderate yield.

Table 2. Reactions of **7** under Ph_3P, CCl_4, and $ZnCl_2$

7 ⟶ **2** + **8**

Entry	$Ph_3P/CCl_4/ZnCl_2$			Conditions (MeCN, Δ, min)		Ratio[a] **2**	**8**	**7**
1	3	10	0	rt	60	-	trace	major
2	2	4	3	rt	180	20	70	10
3	1.2	10	0		20	4	96	-
4	1.2	10	0.2		80	1	92	7
5	2	4	1		10	30	70	-
6	2	4	2		10	58	42	-
7	2	4	3		10	78(52)[b](≥99)[c]	22	-
8	2	4	5		10	76(45) (≥99)	24	-
9	2	4	10		10	75(20) (≥99)	25	-

[a] a ratio of the product mixture by capillary GC.
[b] an isolated yield.
[c] an enantiomeric excess by capillary GC.[11]

In conclusion, we have demonstrated new synthesis of **2** from **7** *via* intramolecular Mitsunobu cyclization reaction in the presence of $ZnCl_2$. We also have found that treatment of **7** with Ph_3P, CCl_4, and $ZnCl_2$ readily permits facile cyclization to **2**. A key feature of this approach is enantioselective cyclization of the primary aromatic amine to form the C-N bond in good yield. Further elaboration as well as examination of other variation of these processes are ongoing.

Acknowledgments: The authors wish to thank the KIST for a financial support.

REFERENCES AND NOTES

1. (a) Hayakawa, I.; Atarashi, S.; Yokohama, S.; Imamura, M.; Sakano, K.; Furukawa, M. *Antimicrob. Agents Chemother.* **1986**, *29*, 163-164. (b) Atarashi, S.; Yokohama, S.; Yamazaki, K.; Sakano, K.; Imamura, M.; Hayakawa, I. *Chem. Pharm. Bull.* **1987**, *35*, 1896-1902. (c) Mitscher, L. A.; Sharma, P. N.; Chu, D. T. W.; Shen, L. L.; Pernet, A. G. *J. Med. Chem.* **1987**, *30*, 2283-2286. (d) Daiichi Seiyaku, *Drugs Future* **1992**, *17*, 559-563.

2. (a) Atarashi, S.; Tsurumi, H.; Fujiwara, T.; Hayakawa, I. *J. Heterocyclic Chem.* **1991**, *28*, 329-331. (b) Sakano, K.; Yokohama, S.; Hayakawa, I.; Atarashi, S.; Kadoya, S. *Agric. Biol. Chem.* **1987**, *51*, 1265-1270. (c) Kuroda, H.; Miyadera, A.; Tojo, Y. Jpn. Kokai Tokkyo Koho JP 01,261,380 [89,261,380], 1989; *Chem. Abstr.* **1990**, *112*, 198397g. (d) Kuroda, H.; Miyadera, A.; Imura, A Jpn. Kokai Tokkyo Koho JP 02,31,695 [90,31,695], 1990; *Chem. Abstr.* **1990**, *113*, 76637k. (e) Fujiwara, T.; Tsurumi, H.; Sato, Y. Eur. Pat. Appl. EP 304,684 (1989); *Chem. Abstr.* **1989**, *111*, 134170z. (f) Fujiwara, T.; Yokota, T. Jpn. Kokai Tokkyo Koho JP 01,175,975 [89,175,975], 1989; *Chem. Abstr.* **1990**, *112*, 35875x. (g) Van Zoest, W.J.; Marx, A.F.; Koger, H.S.; Booy, J. Eur. Pat. Appl. EP 368,410 (1990); *Chem. Abstr.* **1990**, *113*, 172032e.

3. Hayakawa, I.; Hiramitsu, T.; Tanaka, Y. *Chem. Pharm. Bull.* **1984**, *32*, 4907-4913.

4. (a) Csuk, R.; Glanzer, B. I. *Chem. Rev.* **1991**, *91*, 49-97. (b) Servi, S. *Synthesis* **1990**, 1-25. (c) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071-1140.

5. Analytical data of **4** to **9**: Compound **4**: Kugelrohr distillation 75~80 °C/2.5 mmHg, $[\alpha]_D^{24}$ −15.3° (*c* 2.05, $CHCl_3$), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.26 (d, J=6.4 Hz, 3H), 2.87 (d, J=3.4 Hz, 1H, exchangeable with D_2O), 4.08~4.14 (m, 1H), 4.18~4.29 (m, 1H), 4.38~4.42 (m, 1H), 6.98~7.06 (m, 1H), 7.74 (ddd, 1H, J=2.4, 5.3, 9.3 Hz); IR (KBr) 3420, 1540, 1354, 1290, 1060 cm^{-1}; EIMS *m/z* (%) 233 (M^+, 3), 175 (20), 159 (100); Anal calcd for $C_9H_9NO_4F_2$: C, 46.36; H, 3.89; N, 6.01. Found: C, 46.17; H, 3.94; N, 6.03. Compound **5**: $[\alpha]_D^{9}$ +37.5° (*c* 0.24, $CHCl_3$), mp 51.5~52 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 3H, J=6.2 Hz), 2.80~3.92 (m, 4H), 4.05~4.15 (m, 2H), 6.41 (ddd, 1H, J=2.2, 4.8, 9.0 Hz), 6.68~6.77 (m, 1H); IR (KBr): 3380, 3318, 1510, 1490, 1050 cm^{-1}; EIMS *m/z* (%) 203 (M^+, 18), 145 (100); Anal calcd for $C_9H_{11}NO_2F_2$: C, 53.20; H, 5.46; N, 6.89. Found: C, 53.24; H, 5.53; N, 6.78. Compound **6**: $[\alpha]_D^{25}$ −48.4 (*c* 1.0, $CHCl_3$), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.45 (d, 3H, J=6.3 Hz), 3.74 (br s, 2H, exchangeable with D_2O), 4.24~4.32 (m, 2H), 5.47~5.57 (m, 1H), 6.32 (ddd, 1H, J=2.2, 4.8, 8.8 Hz), 6.67 (m, 1H), 7.44 (m, 2H), 7.57 (m, 1H), 8.04 (m, 2H); IR (KBr), 3472, 3374, 1787, 1508, 1276 cm^{-1}; EIMS *m/z* (%) 307 (M^+, 2), 163 (50), 144 (8), 105 (100), 77 (32); Anal calcd for $C_{16}H_{15}NO_3F_2$: C, 62.53; H, 4.93; N, 4.55 Found: C, 62.45; H, 4.86; N, 4.51. Compound **7**: the ^{1}H-NMR spectrum, IR spectrum, TLC behavior, and MS fragmentation were identical with those of the isomer **5**; $[\alpha]_D^{25}$ −37.0° (*c* 1.0, $CHCl_3$), mp 51.5 °C; Anal calcd for $C_9H_{11}NO_2F_2$: C, 53.20; H, 5.46; N, 6.89. Found: C, 53.15; H, 5.50; N, 7.15. Compound **8**: $[\alpha]_D^{13}$ +29.1° (*c* 0.35, $CHCl_3$), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.61 (d, 3H, J=6.6 Hz), 3.90 (br s, 2H, exchangeable with D_2O), 4.08 (dd, 1H, J=7.1, 10.2Hz), 4.23~4.34 (m, 2H), 6.39 (ddd, 1H, J=2.3, 4.8, 9.0 Hz), 6.67~6.76 (m, 1H); IR (KBr): 3470, 3380, 2932, 1602, 1508, 1390, 1264, 1236,1052 cm^{-1}; EIMS *m/z* (%) 221 (M^+, 13), 145 (100), 116 (16); HRMS *m/z* calcd for $C_9H_{10}NOClF_2$ (M^+): 221.0419; found: 221.0418. Compound **9**: $[\alpha]_D^{26}$ +12.9° (*c* 0.63, $CHCl_3$), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.24 (d, 3H, J=6.3 Hz), 1.27~1.33 (m, 6H), 3.75~4.28 (m, 8H), 4.55~4.84 (m, 1H), 6.41 (ddd, 1H, J=2, 5, 9 Hz), 6.65~6.74 (m, 1H), 6.78~6.95 (m, 1H); EIMS *m/z* (%) 361 (M^+, 4), 316 (3), 217 (73), 189 (6), 145 (39), 117 (100); HRMS *m/z* calcd for $C_{15}H_{21}F_2N_3O_5$ (M^+): 361.1449; found: 361.1445.

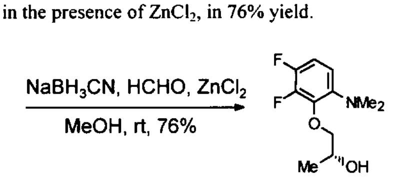
6. The optical purity of **4** was measured by ^{1}H- and ^{19}F-NMR spectroscopy and capillary GC analysis of the corresponding MTPA (Moshers' acid) ester.[12]

7. (a) Mitsunobu, O. *Synthesis*, **1981**,1-28. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335-635. (c) Castro, B.R. *Org. React.* **1983**, *29*, 1-162.

8. Herzig, J.; Nudelman, A.; Gottlieb, H. E.; Fischer, B. *J. Org. Chem.*, **1986**, *51*, 727-730.

9. The enantiomeric excess of 7 was determined by ^{1}H- and ^{19}F-NMR spectroscopy of the corresponding MTPA ester of *N,N*-dimethylanilinoalcohol derivative **10**, which was prepared from 7 by the reductive methylation of an amine[13] with $NaBH_3CN$ and HCHO in the presence of $ZnCl_2$, in 76% yield.

7



10

Analytical data of compound **10**: Kugelrohr distillation 70~80 °C/ 2.5 mmHg, $[\alpha]_D^{26}$ −52.3° (*c* 1.18, $CHCl_3$), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.12 (d, 3H, J=6.3 Hz), 2.76(s, 6H), 3.7~3.78 (m, 1H), 3.83~3.98 (m, 1H), 4.26~4.30 (m, 1H), 6.73 (ddd, 1H, J=2, 5, 9 Hz), 6.83~6.92 (m, 1H); IR (KBr): 3282, 2972, 1502, 1380, 1282, 1060 cm^{-1}; EIMS *m/z* (%) 231 (M^+, 23), 216 (2), 187 (4), 172 (100), 158 (30); HRMS *m/z* calcd for $C_{11}H_{15}NO_2F_2$: (M^+): 231.1071; found: 231.1070.

10. $[\alpha]_D^{22}$ -5.3° (*c* 1.7, $CHCl_3$) [lit., $[\alpha]_D^{23}$ -7.8° (*c* 6.8, $CHCl_3$),[1b] $[\alpha]_D^{25}$ -9.6° (*c* 2.17, $CHCl_3$)[1b]], ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.20 (d, 3H, J=6.3 Hz), 3.45~3.55 (m, 1H), 3.78 (dd, 1H, J=8.3, 10.4 Hz), 4.28 (dd, 1H, J=2.7, 10.4 Hz), 6.25 (ddd, 1H, J=2.3, 4.7, 8.9 Hz), 6.55 (m,1H); EIMS *m/z* 185 (M^+), 170 (100), 156 (13), 142 (20); HRMS *m/z* calcd for $C_9H_9NOF_2$ (M^+): 185.0652; found: 185.0651.

11. The optical purity of the resulting **2** was determined by GC analysis of the corresponding *N*-trifluoroacetamide derivative (M^+ = 281) derived from the benzoxazine derivative **2** and trifluoroacetic anhydride using 50 m × 0.32 mm I.D. PERMABOND L-CHIRASIL-VAL fused silica capillary column with FID. The retention times of **2** and its enantiomer were 62.121 min and 62.798 min, respectively.

12. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.

13. Kim, S.; Oh, C. H.; Ko, J. C.; Ahn, K. H.; Kim, Y. J. *J. Org. Chem.*, **1985**, *50*, 1927-1932.

(*Received in Japan* 30 *September* 1996; *accepted* 11 *November* 1996)