A FACILE AND CONVENIENT SYNTHESIS OF FLUORINE-CONTAINING NAPHTH-[1,2-*d*][1,3]OXAZINES BY NOVEL CYCLIZATION OF *N*,*N*-DIALKYL-2,4-BIS-(TRIFLUOROACETYL)-1-NAPHTHYLAMINES

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Abstract - *N*,*N*-Dialkyl-2,4-bis(trifluoroacetyl)-1-naphthylamines (**1a-j**) underwent acid catalyzed cyclization by trifluoroacetic acid or silica gel to give naphth[1,2-*d*][1,3]oxazines (**2a-j**) in excellent yields. Naphthylamines (**1b,d,e,h-j**) were found to perform this type of cyclization easily in refluxing butyronitrile or acetonitrile even in the absence of acids. Remarkably high regioselectivities were exhibited in the cyclization of unsymmetrically *N*,*N*-dialkyl-substituted naphthylamines (**1g-j**) and the corresponding naphth[1,2-*d*][1,3]oxazines (**2g-j**) were obtained in high yields.

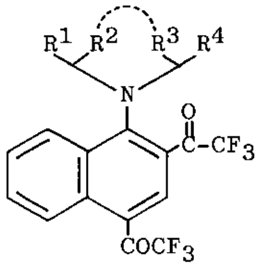
In our preceding communication[1] it has been reported that *N*,*N*-dimethyl- and *N*,*N*-tetramethylene-2,4-bis(trifluoroacetyl)-1-naphthylamines (**1a** and **1c**) undergo the novel acid catalized cyclization to give the corresponding fluorine-containing naphth[1,2-*d*][1,3]-oxazines (**2a** and **2c**), respectively, in excellent yields. In continuation of this work, we have investigated this type of naphthoxazine ring formation reaction in more detail, particularly paying attention to its regioselectivity. These fluorine-containing naphthoxazines (**2**) are expected to have interesting biological activities and have attracted much attention in recent years for their potential utility in medicinal and agricultural sciences.[2-5]

Starting materials (**1a,b,d,e,g-j**) were easily prepared in high yields by the direct bis-trifluoroacetylation of the corresponding N,N-dialkyl-1-naphthylamines with trifluoroacetic anhydride. The trifluoroacetyl group at the 2- or 4-position of compounds (**1e,h,i**) existed partially as hydrated form. Compound (**1c**) was obtained quantitatively by the novel aromatic nucleophilic N-N (dimethylamino-pyrrolidinyl) exchange reaction of **1a** with pyrrolidine.[6] Compound (**1f**) was synthesized in 68% yield by the S-N (p-tolylthio-morpholino) exchange reaction of p-tolyl 2,4-bis(trifluoroacetyl)-1-naphthyl sulfide[7] with morpholine.

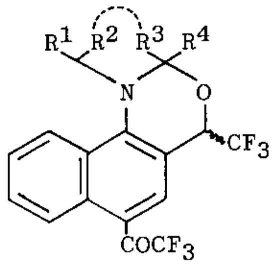
The results of the cyclization of N,N-dialkyl-2,4-bis(trifluoroacetyl)-1-naphthylamines (**1a-j**) into naphth[1,2-d][1,3]oxazines (**2a-j**) are summarized in Table 1. Although the cyclization of dimethylamino derivative (**1a**) into naphthoxazine (**2a**) did not proceed to any appreciable extent for 24 h in refluxing butyronitrile without acid catalysts (Method C), acceleration of the reaction was accomplished by the use of an acid catalyst such as trifluoroacetic acid (Method A) or silica gel (Method B) and **2a** was obtained in high yields (Entries 1-5). Diethylamino derivative (**1b**) exhibited much higher reactivities than **1a** to undergo easily thermally induced cyclization as well as acid catalyzed one (Entries 6-8).

Similarly, cyclization of cyclic amino compounds such as pyrrolidinyl (**1c**), piperidino (**1d**), and perhydroazepinyl (**1e**) derivatives also took place readily under these conditions, except for thermally induced reaction of **1c**, to give the corresponding bicyclic naphthoxazines (**2c-e**) in excellent yields (Entries 9, 11, 12, 14, 16, 18, 20, and 22-24). In both series of reactions carried out on silica gel without solvent and in butyronitrile without catalyst, the reactivity increased in the order of **1c** < **1d** < **1e** (Entries 13, 14, 17, 19, 20, 23, and 24). This is just the order of increasing bulkiness (ring size) of their cyclic amino groups, 5- < 6- < 7-membered rings. In the reaction runned in trifluoroacetic acid, however, the present tendency was completely lost (Entries 10, 15, and 21).

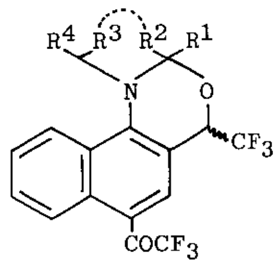
In analogy with piperidine derivative (**1d**), the ring closure of morpholine derivative (**1f**) on silica gel also proceeded cleanly at 80 °C for 24 h to afford the corresponding



1a–j



2a–j



3a–j

1–8	R^1	R^2	R^3	R^4	**1–8**	R^1	R^2	R^3	R^4
a:	H	H	H	H	**f:**	H	$-CH_2OCH_2-$		H
b:	Me	H	Me	H	**g:**	H	H	Me	H
c:	H	$-(CH_2)_2-$		H	**h:**	H	H	Me	Me
d:	H	$-(CH_2)_3-$		H	**i:**	Me	H	Me	Me
e:	H	$-(CH_2)_4-$		H	**j:**	H	$-(CH_2)_2-$		Me

Table 1. Cyclization of N,N-Dialkyl-2,4-bis(trifluoroacetyl)-1-naphthylamines (**1**) into Naphth[1,2-d][1,3]oxazines (**2**)

Entry	Substrate	Method[a]	Temp (°C)	Time (h)	Product	Yield[b] (%)	Ratio of stereoisomers[c]
1	**1a**	A	reflux	24	**2a**	76(19)	–
2[d]		A	reflux	65		98	–
3		B	40	24		90(10)	–
4[d]		B	80	24		93	–
5		C	reflux	24		0(100)	–
6	**1b**	A	reflux	24	**2b**	74	70 : 30
7		B	40	2		100	70 : 30
8		C	reflux	24		100	70 : 30
9[d]	**1c**	A	20	44	**2c**	97	65 : 35
10		A	40	2		69(28)	60 : 40
11[d]		A	reflux	0.5		97	65 : 35
12[d]		B	30	48		100	15 : 85
13		B	40	2		58(42)	5 : 95
14		C	reflux	24		21(79)	45 : 55
15	**1d**	A	40	2	**2d**	12(88)	0 :100
16		A	reflux	24		100	55 : 45
17		B	40	2		78(22)	30 : 70
18		B	40	8		100	30 : 70
19		C	reflux	4		17(83)	45 : 55
20		C	reflux	24		100	45 : 55
21	**1e**	A	40	2	**2e**	73(27)	0 :100
22		A	reflux	0.5		100	15 : 85
23		B	25	2		89	0 :100
24		C	reflux	4		97	45 : 55
25	**1f**	A	40	2	**2f**	0(84)	–
26		A	reflux	24		43 wt%[e]	–[f]
27		B	40	2		0(100)	–
28		B	80	24		99	40 : 60
29		C	reflux	24		21(54)	45 : 55
30	**1g**	A	reflux	24	**2g**	66	40 : 60

Table 1. (Continued)

Entry	Sub-strate	Meth-od[a)]	Temp (°C)	Time (h)	Prod-uct	Yield[b)] (%)	Ratio of stereoisomers[c)]
31	**1g**	B	40	24	**2g**	100	45 : 55
32		C	reflux	24		27(73)	50 : 50
33	**1h**	A	reflux	24	**2h**	91	–
34		B	40	24		92	–
35		D	reflux	24		96	–
36	**1i**	A	reflux	24	**2i**	90	–
37		B	40	24		91	–
38		D	reflux	24		96	–
39	**1j**	A	reflux	24	**2j/3j**	73/24	–[f)]
40		B	40	24		69/9(11)	–[f)]
41		C	reflux	24		80/10	–[f)]

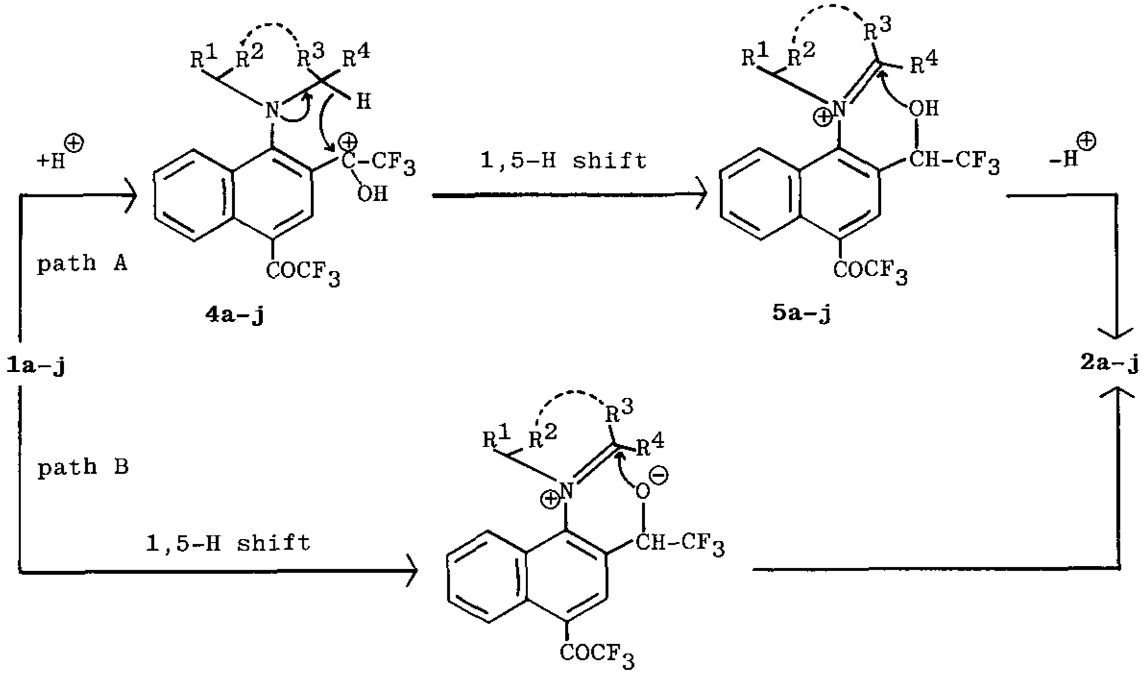
a) Method A: in CF_3CO_2H. Method B: on SiO_2. Method C: in PrCN. Method D: in MeCN. b) Yields of isolated products are shown except for Entries 1, 3, 10, 13-15, 17, 19, 21, 32, and 39-41, where yields are determined by ^{1}H-nmr integration of the mixtures. Values in parentheses are the recovery of **1**. c) Stereochemistry is not determined yet. However, approximate ratios of the two stereoisomers could be estimated by ^{1}H-nmr analysis of the resulted mixtures. One stereoisomer reveals a quartet with H-F coupling of 8 Hz for the benzylic proton (C<u>H</u>CF_3) and the other one shows that of 6 Hz. The former and latter ratios are indicated on the right and left sides, respectively. d) See ref. 1. e) The mixture of **2f** and decomposition products was eluted in 43 wt% yield. Separation of mixtures was unsuccessful. f) The proportions of the stereoisomers could not be estimated exactly because of the extensive overlap of their ^{1}H-nmr signals.

naphthoxazine (**2f**) in 99% yield (Entry 28). The difference in reactivity between **1f** (6-membered ring heterocycle containing a nitrogen atom) and **1d** (that containing both nitrogen and oxygen atoms) was examined. The silica gel catalyzed and thermally induced cyclizations of piperidine derivative (**1d**) showed considerably high conversions more than 78% in striking contrast to low reactivity (conversions of less than 28%) of morpholine derivative (**1f**) (Entries 17, 20, 27, and 29). Corresponding accurate comparison in trifluoroacetic acid (as a solvent) catalyzed cyclization was not made because the reaction of **1f** did not occur under mild conditions (at 40 °C for 2 h) and more forced conditions (under reflux for 24 h) caused increased decomposition of the products (Entries 25 and 26). In order to examine regioselectivity in this type of ring closure reaction, we tried the cyclization of unsymmetrically substituted *N*,*N*-dialkyl-2,4-bis(trifluoroacetyl)-1-naphthylamines (**1g-j**) instead of symmetrically substituted compounds (**1a-f**). The cyclization of *N*-methyl-*N*-ethyl derivative (**1g**) trifluoroacetic acid catalyzed took place exclusively between the methylene of the ethyl group and the carbonyl group (Entry 30). Ring closure of N-methyl-N-isopropyl (**1h**) and N-ethyl-N-isopropyl (**1i**) derivatives occurred in both cases selectively at the methine carbon of the isopropyl group to afford **2h** and **2i** as a single product for each in high yields (Entries 33 and 36). However, this remarkably high regioselectivity was lost to some extent in the reaction of 2-methylpyrrolidinyl derivative (**1j**), where a mixture of **2j** (73%) and its regioisomer (**3j**,[8] 24%) was obtained (Entry 39). Almost the same regioselectivities were observed both in the silica gel catalyzed cyclization (Entries 31, 34, 37, and 40) and in the thermally induced one (Entries 32, 35, 38, and 41). In addition, **1h** and **1i** were found to undergo easily the present ring closure at reflux temperature even in acetonitrile, bp 82 °C (Method D), used as a solvent in place of butyronitrile, bp 117 °C (Entries 35 and 38). These results also demonstrate that in the thermally induced cyclization the increasing order of reactivity is **1a** < **1g** < **1h** (Entries 5, 32, and 35). Consequently, it was found that the reactivity in this cyclization increases in the order of methyl (Me) < methylene (Et) < methine (i-Pr).

Much higher stereoselectivities were exhibited in only some cases of the acid catalyzed cyclizations of cyclic amines (**1c-e**) (Entries 12, 13, 15, and 21-23). In the other cases, however, highly stereoselective cyclizations were not demonstrated.

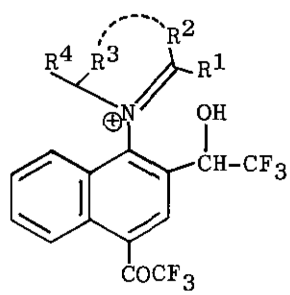
A proposed mechanism for the present cyclization is as shown in Scheme 1. In trifluoroacetic acid and on silica gel (path A), the carbocation (**4**) resulting from protonation of the naphthylamine (**1**) undergoes 1,5-H shift to generate the iminium intermediate (**5**). Subsequently, intramolecular addition of the hydroxy group to the iminium double bond takes place to give the naphthoxazine (**2**). In butyronitrile and in acetonitrile, under non-acidic conditions (path B), the thermal 1,5-H shift occurs to produce the dipolar intermediate (**6**), which undergoes intramolecular nucleophilic attack of the negatively charged oxygen onto the iminium carbon to afford **2**.

The high regioselectivity obtained in the ring closure of unsymmetrically N,N-dialkyl-substituted compounds (**1g-j**) can be rationally explained by making a comparison of the difference in stability between two possible iminium intermediates (**5** vs. **7** or **6** vs. **8**) resulted by 1,5-H shift. The intermediate (**5** or **6**) having more highly substituted iminium double bond is thermodynamically more stable than **7** or **8** having less substituted one,

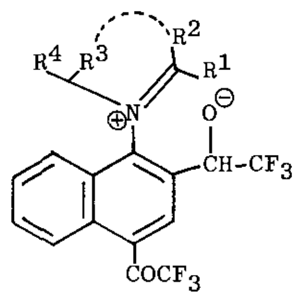


Scheme 1

hence C-O bond formation in this ring closure occurs exclusively or predominantly at more highly branched carbon atom, that is, at the carbon atom bearing R^3 and R^4.



7a-j



8a-j

The foregoing great difference in reactivity between piperidine (**1d**) and morpholine (**1f**) derivatives may be also responsible for the relative stability of the iminium intermediate (5 or 6). The presence of the electronegative oxygen atom in morpholine ring system destabilizes the iminium double bond compared with the methylene at the 4-position in piperidine case on account of the inductive electron-withdrawing effect of the oxygen. Therefore morpholine derivative (**1f**) is less reactive than the corresponding analog (**1d**).

In conclusion, the acid catalyzed or thermally induced cyclization of N,N-dialkyl-2,4-bis(trifluoroacetyl)-1-naphthylamines is a general, experimentally very simple, convenient and therefore very useful process affording in excellent yields CF_3-containing naphthoxazines which are not easily obtained by other methods. Moreover, we have demonstrated that the present ring closure proceeds with remarkably high regioselectivity, when the 2,4-bis(trifluoroacetyl)-1-naphthylamines unsymmetrically N,N-dialkyl-substituted are chosen as starting materials. Our effort is now being directed toward developing new cyclization reactions for constructing naphthalene-fused heterocyclic compounds bearing CF_3 group from 2,4-bis(trifluoroacetyl)-1-naphthylamine precursors. This will be described in our forthcoming papers.

EXPERIMENTAL

Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. Ir spectra were recorded on a Hitachi EPI-G3 spectrophotometer. ^{1}H-Nmr spectra were obtained with a JEOL PMX 60SI instrument using $CDCl_3$ as a solvent unless otherwise indicated. All chemical shifts are reported in ppm downfield from internal tetramethylsilane; coupling constants (J) are given in Hz. Elemental analyses were performed by the Microanalyses Center of Kyoto University. Chromatographic separations were carried out on silica gel column (Wakogel C-200; 100-200 mesh). All chemicals not otherwise mentioned were commercially available and used as such. N,N-Diethyl-1-naphthylamine was prepared from 1-naphthylamine and triethyl phosphate according to literature procedure.[9] N-Ethyl-N-methyl-1-naphthylamine was obtained from N-ethyl-1-naphthylamine and methyl iodide. N-Isopropyl-N-methyl- and N-ethyl-N-isopropyl-1-naphthylamines were prepared from N-isopropyl-1-naphthylamine, which was obtained from 1-naphthylamine and isopropyl iodide, and subsequent treatment with methyl and ethyl iodides, respectively. N,N-Pentamethylene-, N,N-hexamethylene-, and N,N-(1-methyltetramethylene)-1-naphthylamines were synthesized from 1-naphthylamine and 1,5-dibromopentane, 1,6-dibromohexane, and 1,4-dibromopentane, respectively. Final purification of all products for elemental analyses was done by recrystallization.

General Procedure for the Synthesis of N,N-Dialkyl-2,4-bis(trifluoroacetyl)-1-naphthyl-

amines (1a,b,d,e,g-j). To a solution of N,N-dialkyl-1-naphthylamines (5 mmol) and pyridine (900 mg, 12.5 mmol) in $CHCl_3$ (10 ml) was added trifluoroacetic anhydride (2630 mg, 12.5 mmol) and the solution was stirred at room temperature for 18 h. After addition of CH_2Cl_2 (100 ml), the mixture was washed once with 1 N HCl (100 ml), once with water (100 ml), and subsequently dried (Na_2SO_4). The solvent was evaporated to give the practically pure product.

Compounds (**1e,h,i**) are hydrated partially at the 2- or 4-trifluoroacetyl group and therefore purification for microanalysis of these compounds was difficult. The structural assignment was confirmed by ^{1}H-nmr of the crude products.

1a: yield 100%; mp 87-88 °C (hexane/benzene); ir (KBr) 1690 cm^{-1}; ^{1}H-nmr 8.97-8.70 (m, 1H, H-5), 8.37 (br s, 1H, H-3), 8.23-7.95 (m, 1H, H-8), 7.73-7.28 (m, 2H, H-6, -7), 3.17 (s, 6H, NCH_3). Anal. Calcd for $C_{16}H_{11}NO_2F_6$: C, 52.90; H, 3.05; N, 3.86; F, 31.38. Found: C, 52.99; H, 3.00; N, 4.10; F, 31.10.

1b: yield 100%; mp 53-54 °C (hexane/benzene); ir (KBr) 1691 cm^{-1}; ^{1}H-nmr 8.92 (dd, J=2, 8, 1H, H-5), 8.37-8.10 (m, 2H, H-3, -8), 7.82-7.33 (m, 2H, H-6, -7), 3.45 (q, J=7, 4H, CH_2), 1.22 (t, J=7, 6H, CH_3). Anal. Calcd for $C_{18}H_{15}NO_2F_6$: C, 55.25; H, 3.86; N, 3.58. Found: C, 55.53; N, 3.82; N, 3.55.

1d: yield 98%; mp 107-108 °C (hexane/$CHCl_3$); ir (KBr) 1710 cm^{-1}; ^{1}H-nmr 8.87 (dd, J=2, 8, 1H, H-5), 8.30-8.07 (m, 2H, H-3, -8), 7.77-7.33 (m, 2H, H-6, -7), 3.47-2.90 (br, 4H, CH_2NCH_2), 2.27-1.50 (br, 6H, $NCH_2(C\underline{H}_2)_3$). Anal. Calcd for $C_{19}H_{15}NO_2F_6$: C, 56.58; H, 3.75; N, 3.47; F, 28.26. Found: C, 56.67; H, 3.64; N, 3.37; F, 28.54.

1e (partially hydrated): yield 100%; yellow solid; ^{1}H-nmr ($CDCl_3$-D_2O) 8.85-8.52(m, 1H, H-5), 8.35 (br s, 1H, H-3), 8.22-7.32 (m, 3H, H-6, -7, -8), 3.55-3.05 (br, 4H, CH_2NCH_2), 2.42-1.48 (br, 8H, $NCH_2(C\underline{H}_2)_4$).

1g: yield 98%; mp 83-84 °C (hexane); ir (KBr) 1682 cm^{-1}; ^{1}H-nmr 8.93-8.77 (m, 1H, H-5), 8.33 (br s, 1H, H-3), 8.20-8.03 (m, 1H, H-8), 7.77-7,33 (m, 2H, H-6, -7), 3.40 (q, J=7, 2H, NCH_2), 3.03 (s, 3H, NCH_3), 1.30 (t, J=7, 3H, $NCH_2C\underline{H}_3$). Anal. Calcd for $C_{17}H_{13}NO_2F_6$: C, 54.12; H, 3.47; N, 3.71: F, 30.21. Found: C, 54.15; H, 3.43; N, 3.84; F, 30.41.

1h (partially hydrated): yield 100%; yellow solid; ^{1}H-nmr ($CDCl_3$-D_2O) 8.97-8.60 (m, 1H, H-5), 8.39-7.97 (m, 2H, H-3, -8), 7.79-7.37 (m, 2H, H-6, -7), 4.03 (hp, J=6, 1H, CH), 3.53-2.87 (m, 3H, NCH_3), 1.70-0.67 (m, 6H, $CH(C\underline{H}_3)_2$).

1i (partially hydrated): yield 100%; yellow solid; ^{1}H-nmr ($CDCl_3$-D_2O) 8.92-7.39 (m, $5H_{arom}$), 4.25-3.15 (m, 3H, CH_2NCH), 1.85-0.72 (m, 9H, $C\underline{H}_3CH_2NCH(C\underline{H}_3)_2$).

1j: yield 99%; mp 137-138 °C (hexane/$CHCl_3$); ir (KBr) 1643 cm^{-1}; ^{1}H-nmr 8.75 (dd, J=2, 8, 1H, H-5), 8.42 (br s, 1H, H-3), 7.90-7.07 (m, 3H, H-6, -7, -8), 5.23-4.53 (br, 1H, $NC\underline{H}CH_3$), 3.93-2.73 (br m, 2H, NCH_2), 2.60-1.60 (br, 4H, $NCH_2(C\underline{H}_2)_2$), 1.42 (d, J=6, 3H, CH_3). Anal. Calcd for $C_{19}H_{15}NO_2F_6$: C, 56.58, H, 3.75; N, 3.47; F, 28.26. Found: C, 56.41, H, 3.61; N, 3.41; F, 28.00.

Procedure for the Synthesis of 1c.[6] To a solution of **1a** (1816 mg, 5 mmol) in MeCN (20 ml) was added pyrrolidine (370 mg, 5.2 mmol). The mixture was stirred at reflux temperature for 24 h. Evaporation of the solvent afforded **1c** (1950 mg, 100%): mp 158-159 °C (hexane/benzene); ir (KBr) 1646 cm^{-1}; ^{1}H-nmr 8.88-8.72 (m, 1H, H-5), 8.48 (br s, 1H, H-3), 7.90-7.73 (m, 1H, H-8), 7.67-7.14 (m, 2H, H-6, -7), 3.77-3.55 (m, 4H, CH_2NCH_2), 2.12-1.89 (m, 4H, $NCH_2(C\underline{H}_2)_2$). Anal. Calcd for $C_{18}H_{13}NO_2F_6$: C, 55.54, H, 3.37; N, 3.60; F, 29.28. Found: C, 55.63; H, 3.13; N, 3.52; F, 28.98.

Procedure for the Synthesis of 1f. To a solution of p-tolyl 2,4-bis(trifluoroacetyl)-1-naphthyl sulfide[7] (582 mg, 1.3 mmol) in MeCN (10 ml) was added morpholine (340 mg, 3.9 mmol) and the mixture was refluxed for 18 h. The solvent was removed under reduced pressure, the crude mixture was purified by chromatography using benzene as eluent to give **1f** (361 mg, 68%): mp 142-143 °C (hexane/$CHCl_3$); ir (KBr) 1730, 1700 cm^{-1}; ^{1}H-nmr 8.90-8.72 (m, 1H, H-5), 8.43-8.05 (m, 2H, H-3, -8), 7.83-7.40 (m, 2H, H-6, -7), 3.93 (t, J=4, 4H, CH_2OCH_2), 3.27 (t, J=4, 4H, CH_2NCH_2). Anal. Calcd for $C_{18}H_{13}NO_3F_6$: C, 53.34, H, 3.23, N, 3.46; F, 28.12. Found: C, 53.38, H, 3.13; N, 3.46; F, 28.06.

General Procedure for the Cyclization of N,N-Dialkyl-2,4-bis(trifluoroacetyl)-1-naphthylamines (1) into Naphth[1,2-d][1,3]oxazines (2) (Refer to Table 1). Method A: A solution of **1** (2 mmol) in trifluoroacetic acid (6840 mg, 60 mmol) was stirred at 20 °C, 40 °C or at reflux temperature for 0.5-65 h. After addition of CH_2Cl_2 (100 ml), the mixture was washed once with 20% aq. Na_2CO_3 (100 ml), once with water (100 ml), and subsequently dried (Na_2SO_4). The solvent was evaporated to give the practically pure product. In Entry 6 the crude product was purified by ball-tube distillation (150 °C/4 torr) to give **2b** (74%).

In Entry 25 substrate (**1**) was recovered in 84% yield by chromatography using benzene/ethyl acetate (7:3). In Entry 26 the crude product was purified by chromatography using hexane/ benzene (3:7) to give the mixture of **2f** and decomposition products (43 wt%). In Entry 30 the crude product was purified by chromatography using hexane/benzene (3:2) to give **2g** (66%). In Entry 39 the crude product was purified by chromatography using hexane/ benzene (3:1) to afford the mixture of **2j** (73%) and **3j**[8] (24%). **Method B:** Dry silica gel (4000 mg, Wakogel C-200 for column chromatography dried at 180 °C for 2 h under reduced pressure just before use) and a solution of **1** (400 mg) in CH_2Cl_2 (20 ml) were combined and the whole mixture was stirred well and the solvent was thoroughly removed in vacuo. Thus obtained yellow powder was allowed to stand at 25-80 °C for 2-48 h under nitrogen atmosphere. To this was added CH_2Cl_2 (50 ml) and the mixture was stirred for 10 min. Silica gel was filtered off and washed with CH_2Cl_2 (50 ml). The filtrate and the washings were combined, dried over Na_2SO_4, and the solvent was evaporated to give the practically pure product. **Method C:** A solution of **1** (2 mmol) in PrCN (8 ml) was refluxed for 4 h or 24 h and the solvent was removed under reduced pressure to give the practically pure product. In Entry 29 the crude products were separated by chromatography as eluted with benzene for **2f** (21%) and benzene/ethyl acetate (7:3) for recovered substrate (**1**) (54%). In Entry 41 the crude product was purified by chromatography to afford the mixture of **2j** (80%) and **3j** (10%). **Method D:** Reactions were carried out according to Method C except that MeCN was used as solvent instead of PrCN.

Attempted fractionation of the two stereoisomers (**2b,c,d,f,g**) by tlc failed owing to the very small differences of their polarities. In cases of **2e** and **2j**, pure stereoisomers could be obtained by recrystallization in each case.

2a: mp 103-104 °C (Spectroscopic and analytical data are described in ref. 1.)

2b (mixture of stereoisomers): mp 85-93 °C (hexane); ir (KBr) 1701 cm^{-1}; ^{1}H-nmr 9.06-8.80 (m, 1H, H-7), 8.27-8.07 (m, 2H, H-5, -10), 7.81-7.42 (m, 2H, H-8, -9), 5.44 (q, J=6, 0.2H, H-4), 5.29 (q, J=8, 0.8H, H-4), 5.17 (q, J=6, 0.8H, H-2), 4.89 (q, J=6, 0.2H, H-2), 3.94-3.07 (m, 2H, NCH_2), 1.67 (d, J=6, 0.6H, CH_3-2), 1.51 (d, J=6, 2.4H, CH_3-2), 1.32 (t, J=7, 0.6H, $NCH_2C\underline{H}_3$), 1.28 (t, J=7, 2.4H, $NCH_2C\underline{H}_3$). Anal. Calcd for $C_{18}H_{15}NO_2F_6$: C, 55.25; N, 3.86; H, 3.58; F, 29.13. Found: C, 55.06; H, 3.99; N, 3.67; H, 29.01.

2c (mixture of stereoisomers): mp 90-105 °C (hexane); ir (KBr) 1685 cm^{-1}; ^1H-nmr 8.93-8.70 (m, 1H, H-8), 8.10-7.93 (m, 2H, H-6, -11), 7.80-7.27 (m, 2H, H-9, -10), 5.32 (q, J=6, 0.35H, H-5), 5.17 (br s, 0.65H, H-3a), 5.07 (q, J=8, 0.65H, H-5), 4.87 (br s, 0.35H, H-3a), 4.27-3.87 (m, 1H, H-1), 3.70-3.20 (m, 1H, H-1), 2.70-1.70(m, 4H, H-2, -3). Anal. Calcd for $C_{18}H_{13}NO_2F_6$: C, 55.54; H, 3.37; N, 3.60; F, 29.28. Found: C, 54.96, H, 3.21; N, 3.69; F, 28.83.

2d (mixture of stereoisomers): mp 122-125 °C (hexane); ir (KBr) 1708 cm^{-1}; ^1H-nmr 8.98-8.81 (m, 1H, H-9), 8.35-8.14 (br m, 2H, H-7, -12), 7.81-7.49 (m, 2H, H-10, -11), 5.51 (q, J=6, 0.5H, H-6), 5.31 (q, J=8, 0.5H, H-6), 5.03 (br s, 0.5H, H-4a), 4.76 (br s, 0.5H, H-4a), 3.78-2.51 (br, 2H, H-1), 2.51-1.11 (br, 6H, H-2, -3, -4). Anal. Calcd for $C_{19}H_{15}NO_2F_6$: C, 56.58; H, 3.75; N, 3.47; F, 28.26. Found: C, 56.78; H, 3.59; N, 3.51; F, 28.30.

2e (either of stereoisomers): mp 138-139 °C (hexane); ir (KBr) 1706 cm^{-1}; ^1H-nmr 8.90-8.70 (m, 1H, H-10), 8.30-7.90 (m, 2H, H-8, -13), 7.77-7.33 (m, 2H, H-11, -12), 5.35 (q, J=6, 1H, H-7), 4.80-4.58 (m, 1H, H-5a), 3.93-3.03 (br m, 2H, H-1), 2.77-1.17 (br m, 8H, H-2, -3, -4, -5). Anal. Calcd for $C_{20}H_{17}NO_2F_6$: C, 57.56; H, 4.11; N, 3.36; F, 27.31. Found: C, 57.42; H, 4.13; N, 3.41; F, 27.36.

2f (mixture of stereoisomers): 145-149 °C (hexane); ir (KBr) 1706 cm^{-1}; ^1H-nmr 8.90-8.60 (m, 1H, H-9), 8.33-7.93 (m, 2H, H-7, -12), 7.80-7.37 (m, 2H, H-10, -11), 5.52 (q, J=6, 0.6H, H-6), 5.32 (q, J=8, 0.4H, H-6), 4.87-4.70 (br, 0.4H, H-4a), 4.66-4.47 (br, 0.6H, H-4a), 4.40-3.77 (m, 4H, H-2, -4), 3.57-3.10 (m, 2H, H-1). Anal. Calcd for $C_{18}H_{13}NO_3F_6$: C, 53.34; H, 3.23; N, 3.46; F, 28.12. Found: C, 52.80; H, 3.27; N, 3.60; F, 27.81.

2g (mixture of stereoisomers): mp 74-84 °C (hexane); ir (KBr) 1705 cm^{-1}; ^1H-nmr 8.82-8.66 (m, 1H, H-7), 8.16-7.80 (m, 2H, H-5, -10), 7.65-7.33 (m, 2H, H-8, -9), 5.35 (q, J=6, 0.6H, H-4), 5.15 (q, J=8, 0.4H, H-4), 4.98 (q, J=6, 0.4H, H-2), 4.72 (q, J=6, 0.6H, H-2), 2.97 (s, 1.8H, NCH_3), 2.93 (s, 1.2H, NCH_3), 1.27 (d, J=6, 1.8H, CH_3-2), 1.22 (d, J=6, 1.2H, CH_3-2). Anal. Calcd for $C_{17}H_{13}NO_2F_6$: C, 54.12; H, 3.47; N, 3.71; F, 30.21. Found: C, 54.09; H, 3.60; N, 3.75; F, 30.13.

2h: mp 125-126 °C (hexane); ir (KBr) 1705 cm^{-1}; ^1H-nmr 8.92-8.75 (m, 1H, H-7), 8.26-8.00 (m, 2H, H-5, -10), 7.74-7.50 (m, 2H, H-8, -9), 5.27 (q, J=6, 1H, H-4), 2.97 (s, 3H, NCH_3), 1.70 (s, 3H, CH_3-2), 1.42 (s, 3H, CH_3-2). Anal. Calcd for $C_{18}H_{15}NO_2F_6$: C, 55.25; H, 3.86; N, 3.58; F, 29.13. Found: C, 55.05; H, 3.99; N, 3.28; F, 29.04.

2i: mp 119-120 °C (hexane); ir (KBr) 1701 cm^{-1}; ^1H-nmr 9.02-8.67 (m, 1H, H-7), 8.27-8.03 (m, 2H, H-5, -10), 7.80-7.33 (m, 2H, H-8, -9), 5.25 (q, J=6, 1H, H-4), 4.03-2.93 (m, 2H, NCH_2), 1.73 (s, 3H, CH_3-2), 1.43 (s, 3H CH_3-2), 1.20 (t, J=7, 3H, $NCH_2C\underline{H}_3$). Anal. Calcd for $C_{19}H_{17}NO_2F_6$: C, 56.30; H, 4.23; N, 3.46; F, 28.18. Found: C, 56.28; H, 4.15; N, 3.66; F, 28.03.

2j (either of stereoisomers): mp 129-130 °C (hexane); ir (KBr) 1692; ^1H-nmr 9.03-8.80 (m, 1H, H-8), 8.30-7.93 (m, 2H, H-6, -11), 7.73-7.33 (m, 2H, H-9, -10), 5.30 (q, J=6, 1H, H-5), 4.40-3.83 (br m, 1H, H-1), 3.70-3.27 (br m, 1H, H-1), 2.73-1.60 (br m, 4H, H-2, -3), 1.47 (s, 3H, CH_3-3a). Anal. Calcd for $C_{19}H_{15}NO_2F_6$: C, 56.58; H, 3.75; N, 3.47; F, 28.26. Found: C, 56.32; H, 3.61; N, 3.49; F, 28.13.

REFERENCES

1. M. Hojo, R. Masuda, and E. Okada, Tetrahedron Lett., 1988, 29, 4599.
2. R. Filler, 'Organofluorine Chemicals and Their Industrial Applications,' ed. by R. E. Banks, Ellis Horwood, London, 1979.
3. R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry,' Kodansha & Elsevier Biomedical, Tokyo, 1982.
4. J. T. Welch, Tetrahedron, 1987, 43, 3123.
5. Z. Eckstein and T. Urbanski, Adv. Heterocycl. Chem., 1978, 23, 1.
6. M. Hojo, R. Masuda, and E. Okada, Tetrahedron Lett., 1987, 28, 6199.
7. M. Hojo, R. Masuda, E. Okada, and H. Miya, Synthesis, 1989, 870.
8. Although **3j** could not be isolated from the mixture by tlc and repeated recrystallizations, the formation of two kinds of stereoisomers (**3j**) was confirmed by careful ^1H-nmr analysis of the resulted reaction mixture. One showed diagnostic absorption for H-11 at 8.35-8.18 (m), that for H-5 at 5.18 (q, J_{HF}=6), and that for CH_3-1 at 1.32 (d, J=6), the other exhibited a characteristic signal for CH_3-1 at 1.05 (d, J=6).
9. J. H. Billman, A. Radike, and B. W. Mundy, J. Am. Chem. Soc., 1942, 64, 2977.

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