A CONVENIENT SYNTHESIS OF FLUORINE-CONTAINING 2,5-EPOXYNAPHTH[1,2-*b*]AZEPINES BY THERMALLY INDUCED CYCLIZATION OF *N*-ALLYL SUBSTITUTED 2,4-BIS(TRIFLUOROACETYL)-1-NAPHTHYLAMINES

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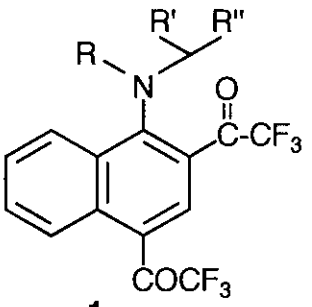
Abstract - Thermally induced cyclization of *N*-allyl substituted 2,4-bis-(trifluoroacetyl)-1-naphthylamines (**4**) proceeded easily in refluxing butyronitrile to give the corresponding 7-trifluoroacetyl-5-trifluoromethyl-2,5-epoxynaphth-[1,2-*b*]azepines (**5**) in excellent yields.

Azepine and the related derivatives constitute an important class of heterocyclic compounds and the skeleton is a component of natural products such as ribasine, balanol, etc., showing interesting bioactive properties.[1] Besides, recently much attention has been paid to the development of new methodologies for the syntheses of many kinds of fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials exhibiting significant biological activities for their potential use in medicinal and agricultural scientific fields.[2] Furthermore, in the course of our ongoing investigations on novel aromatic nucleophilic substitutions[3] and their synthetic applications[4] to the construction of various naphthalene-fused heterocycles bearing trifluoromethyl groups, we have recently reported that *N*,*N*-dialkyl-2,4-bis(trifluoroacetyl)-1-naphthylamines (**1**) undergo novel cyclizations to give the corresponding fluorine-containing naphth[1,2-*d*][1,3]oxazines (**2**)[5] and naphth[1,2-*d*][1,3]thiazines (**3**)[6] in high yields. In connection with these works, we now communicate thermally induced cyclization of *N*-allyl substituted 2,4-bis(trifluoroacetyl)-1-naphthylamines (**4**), in which the products were not *expected* naphth[1,2-



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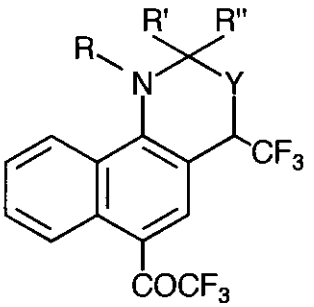
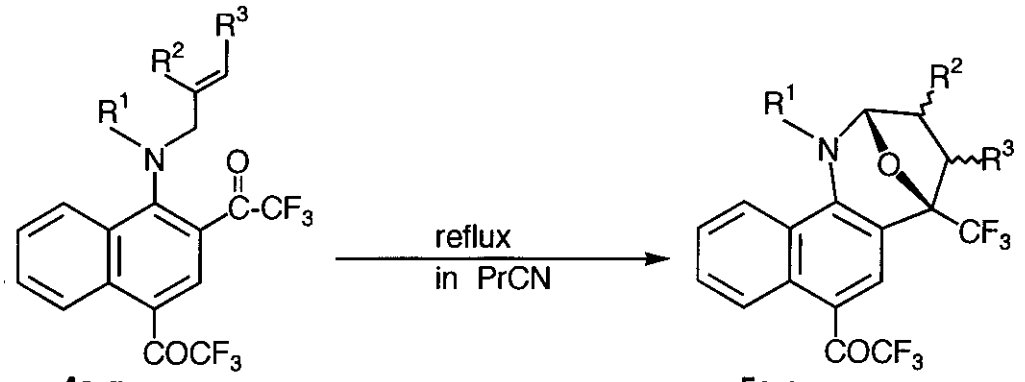


2: Y=O
3: Y=S

d][1,3]oxazines (**2**: e.g., R=Me, R'=vinyl, R"=H) , but *unexpected* 2,5-epoxynaphth[1,2-*b*]azepines (**5**). In a typical experiment, a solution of *N*-allyl-*N*-methyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**4a**)[7] (389 mg, 1.0 mmol) in butyronitrile (4 mL) was refluxed for 24 h with stirring. The solvent was removed *in vacuo* to give 7-trifluoroacetyl-5-trifluoromethyl-1-methyl- 2,5-epoxynaphth[1,2-*b*]azepine derivative (**5a**) quantitatively. The results are summarized and shown in Table 1. Quite similarly, *N*-ethyl derivative (**4b**) underwent the present cyclization to afford the corresponding epoxynaphthazepine (**5b**) in quantitative yield without any formation of expected naphth[1,2-*d*][1,3]oxazine (**2**: R=Et, R'=vinyl, R"=H). It needed heating for longer time (72 h) to complete the reaction of *N*-unsubstituted derivative (**4c**), but the desired



4a-g **5a-g**

4, 5	R^1	R^2	R^3	4, 5	R^1	R^2	R^3
a:	Me	H	H	**e**:	Me	Cl	H
b:	Et	H	H	**f**:	Me	H	Me
c:	H	H	H	**g**:	Me	H	Ph
d:	Me	Me	H				

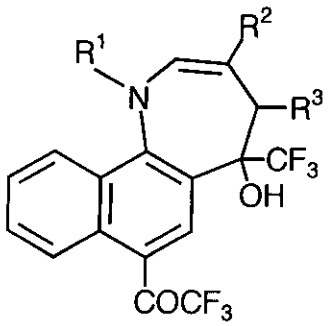
Table 1. Thermally Induced Cyclization of **4** into **5**[a)]

Entry	Substrate	Time(h)	Product	Yield[b)](%)	*endo* : *exo*[c)]
1	**4a**	24	**5a**	100	–
2	**4b**	24	**5b**	100	–
3	**4c**	72	**5c**	83	–
4	**4d**	24	**5d**	100	55 : 45
5	**4e**	24[d)]	**5e**	86	60 : 40
6	**4f**	24	**5f**	22[e)]	0 : 100
7	**4g**	24	**5g**	70[f)]	0 : 100

a) Unless otherwise noted, **4** (1 mmol) was heated under reflux for indicated reaction time in butyronitrile (4 mL). b) Isolated yields. c) Determined by ^{1}H-NMR (250 MHz) analysis. d) Mesitylene was used as a solvent instead of butyronitrile. e) With 67 wt% yield of unknoun products. f) With 21% yield of **2** (R = Me, R' = CH=CHPh, R" = H).

5c was obtained in 83% yield. In analogy with **4a**, the cyclization of *N*-(2-methylallyl) derivative (**4d**) also proceeded easily to provide the mixture of *endo*- and *exo*-**5d** (11:9) in 100% yield. In the case of *N*-(2-chloroallyl) derivative (**4e**), heating at higher temperature (in refluxing mesitylene) was required and afforded 86% yield of **5e** [*endo*/*exo* (3 : 2)]. Interestingly, cyclizations of *N*-(3-methylallyl) and *N*-(3-phenylallyl) derivatives (**4f** and **4g**) exhibited much high stereoselectivity and the *exo*-isomers (**5f** and **5g**) were formed exclusively in 22% and 70% yields, although accompanied by 67 wt% of unknown products and 21% of naphthoxazine (**2**: R=Me, R'=styryl, R"=H)), respectively.

A speculated reaction mechanism for the formation of the present tetrahydroepoxyazepine ring system is as follows: Like ene reaction, carbon-carbon bond formation between the terminal olefinic carbon of *N*-allyl group and carbonyl carbon of trifluoroacetyl group of **4** occurs to give intermediary dihydroazepine derivative (**6**), in which nucleophilic attack of hydroxy oxygen to the olefinic carbon bonded to nitrogen atom takes place to afford bridged end product (**5**) .



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The structures of compounds (**5a-g**) were determined on the basis of their ^{1}H-NMR and IR spectra, together with elemental analyses. As a representative case, **5b** was further confirmed by ^{13}C-NMR spectral data.[8] ^{13}C-NMR spectrum of **5b** showed a doublet for bridgehead *O*,*N*-acetal carbon at 90.0 ppm and a quartet (J_{CF}=30.5 Hz) for the other one bearing

a trifluoromethyl group at 82.7 ppm. ^{1}H-NMR spectra provided diagnostic information for the assignment of stereochemistry. In ^{1}H-NMR spectra of **5d** and **5e**, the bridgehead H-2 of *endo*-isomer appears as doublet with large vicinal H_2-H_3 coupling constant (6.8 and 6.4 Hz, respectively) and that of *exo*-one as singlet. Distinct through-space H-F coupling (1.9 Hz) with $C\underline{F}_3$-5 was observed for $C\underline{H}_3$-4 of *exo*-**5f**. Moreover, stereochemical configuration of *exo*-**5g** was determined by judging from its vicinal H_2-H_3 and H_3-H_4 coupling constants.

Thus, the present synthetic method provides a simple and convenient access to 2,5-epoxynaphth-[1,2-*b*]azepines having trifluoromethyl groups which are not easily obtained by other methods. Further works are now undertaken in our laboratory, together with some experiments from mechanistic standpoint of view.

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7. Substrates (**4a**,**b**,**d-g**) were easily prepared by bis(trifluoroacetylation) of the corresponding *N*-allyl substituted *N*-alkyl-1-naphthylamines with trifluoroacetic anhydride in the usual manner.[5b] Substrate (**4c**) was obtained *via* the novel aromatic nucleophilic substitution (dimethylamino-allylamino exchange reaction) of *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine with allylamine.[3a]
8. **5a**: mp 102-103 ℃; ^{1}H-NMR (δ , 250 MHz, $CDCl_3$): 8.98 (d, 1H, J=8.6 Hz, H-8), 8.23 (s, 1H, H-6), 8.16 (d, 1H, J=8.2 Hz, H-11), 7.72-7.58 (m, 2H, H-9, -10), 5.46 (br d, 1H, J=6.4 Hz, H-2), 3.22 (s, 3H, CH_3), 2.56-2.32 (m, 3H, H-3, -4), 2.19-1.99 (m, 1H, H-3 or -4); IR (KBr) 1704 cm^{-1}; Anal. Calcd for $C_{18}H_{13}NO_2F_6$: C, 55.54; H, 3.37; N, 3.60 ; F, 29.28. Found: C, 55.58; H, 3.26; N, 3.59; F, 29.23. **5b**: mp 126-127 ℃; ^{1}H-NMR (δ , 60 MHz, $CDCl_3$): 9.00-8.70 (m, 1H, H-8), 8.10-7.76 (m, 2H, H-6, -11), 7.73-7.23 (m, 2H, H-9, -10), 5.50 (d, 1H, J=5 Hz, H-2), 3.60-3.20 (m, 2H, NCH_2), 2.73-1.73 (m, 4H, H-3, -4), 1.39 (t, 3H, J=7 Hz, CH_3); ^{13}C-NMR (δ , $CDCl_3$): 180.7 (q, J_{CF}=33.0 Hz), 149.8 (s), 132.7 (s), 129.9 (d), 128.7 (s), 127.8 (d), 126.8 (d), 126.1 (d), 124.8 (q, J_{CF}=280.8 Hz), 124.2 (d), 121.8 (s), 120.6 (s), 117.0 (q, J_{CF}=293.0 Hz), 90.0 (d), 82.7 (q, J_{CF}=30.5 Hz), 51.5 (t), 39.4 (t), 30.7 (t), 14.0 (q); IR (KBr): 1696 cm^{-1}; Anal. Calcd for $C_{19}H_{15}NO_2F_6$: C, 56.58; H, 3.75; N, 3.47 ; F, 28.26. Found: C, 56.74; H, 3.69; N, 3.56; F, 28.29. **5c**: mp 178-179 ℃; ^{1}H-NMR (δ , 60 MHz, CD_3CN): 9.10 (dd, 1H, J=2, 7 Hz, H-8), 8.15 (br s, 1H, H-6), 7.93-7.30 (m, 4H, H-9, -10, -11, NH), 5.75 (br t, 1H, J=4 Hz, H-2), 2.73-2.33 (m, 4H, H-3 or -4); IR (KBr): 3420, 1677 cm^{-1}; Anal. Calcd for $C_{17}H_{11}NO_2F_6$: C, 54.41; H, 2.95; N, 3.73. Found: C, 54.11; H, 2.79; N, 3.83. **5d** (mixture of stereoisomers): mp 109-123 ℃; ^{1}H-NMR (δ , 250 MHz, $CDCl_3$): 9.02-8.96 (m, 1H, H-8), 8.20-8.15 (m, 2H, H-6,

-11), 7.72-7.57 (m, 2H, H-9, -10), 5.38 (d, 0.55H, J=6.8 Hz, H-2), 4.99 (s, 0.45H, H-2), 3.25 (s, 1.65H, NCH_3), 3.21 (s, 1.35H, NCH_3), 2.97-2.78 (m, 0.55H, H-3), 2.70 (dd, 0.55H, J=11.6, 11.8 Hz, H-4), 2.62-2.46 (m, 0.90H, H-3, -4), 2.06-1.95 (m, 0.45H, H-4), 1.89 (dd, 0.55H, J=3.0, 11.6 Hz, H-4), 1.28 (d, 1.35H, J=6.7 Hz, CH_3-3), 1.00 (d, 1.65H, J=7.2 Hz, CH_3-3); IR (KBr): 1691 cm^{-1}; Anal. Calcd for $C_{19}H_{15}NO_2F_6$: C, 56.58; H, 3.75; N, 3.47 ; F, 28.26. Found: C, 56.72; H, 3.69; N, 3.52; F, 27.99. **5e** (mixture of stereoisomers): mp 162-165 ℃; ^{1}H-NMR (δ, 250 MHz, $CDCl_3$): 9.00-8.93 (m, 1H, H-8), 8.26-8.13 (m, 2H, H-6, -11), 7.75-7.60 (m, 2H, H-9, -10), 5.59 (d, 0.6H, J=6.4 Hz, H-2), 5.49 (s, 0.4H, H-2), 4.70 (ddd, 0.6H, J=2.4, 6.4, 10.8 Hz, H-3), 4.49 (dd, 0.4H, J=6.0, 6.8 Hz, H-3), 3.32 (s, 1.8H, NCH_3), 3.27 (s, 1.2H, NCH_3), 3.08 (dd, 0.6H, J=10.8, 13.2 Hz, H-4), 3.07 (dd, 0.4H, J=6.8, 12.7 Hz, H-4), 2.71 (dd, 0.4H, J=6.0, 12.7 Hz, H-4), 2.50 (dd, 0.6H, J=2.4, 13.2 Hz, H-4); IR (KBr): 1697, 1670 cm^{-1}; Anal. Calcd for $C_{18}H_{12}NO_2ClF_6$: C, 51.02; H, 2.85; N, 3.31 ; Cl, 8.37; F, 26.90. Found: C, 50.78; H, 2.75; N, 3.35; Cl, 8.48; F, 26.69. **5f** (*exo*): bp 160 ℃/5 mmHg (oven temperature); ^{1}H-NMR (δ, 250 MHz, $CDCl_3$): 8.97 (d, 1H, J=8.4 Hz, H-8), 8.21 (s, 1H, H-6), 8.15 (d, 1H, J=8.8 Hz, H-11), 7.72-7.58 (m, 2H, H-9, -10), 5.43 (br d, 1H, J=6.8 Hz, H-2), 3.21 (s, 3H, NCH_3), 2.79-2.73 (m, 1H, H-4), 2.28-2.19 (m, 1H, H-3), 2.01-1.93 (m, 1H, H-3), 1.21 (dq, 3H, J=6.8 Hz, J_{HF}=1.9 Hz, CH_3-4); IR (film): 1698 cm^{-1}; Anal. Calcd for $C_{19}H_{15}NO_2F_6$: C, 56.58; H, 3.75; N, 3.47 ; F, 28.26. Found: C, 56.68; H, 3.65; N, 3.46; F, 28.13. **5g** (*exo*): mp 160-161 ℃; ^{1}H-NMR (δ, 250 MHz, $CDCl_3$): 8.98 (d, 1H, J=8.4 Hz, H-8), 8.33 (s, 1H, H-6), 8.21 (d, 1H, J=8.4 Hz, H-11), 7.75-7.61 (m, 2H, H-9, -10), 7.32 (s, 5H, C_6H_5), 5.72 (dd, 1H, J=1.8, 6.7 Hz, H-2), 3.84 (dd, 1H, J=2.1, 8.0 Hz, H-4), 3.30 (s, 3H, CH_3), 2.66 (ddd, 1H, J=2.1, 6.7, 14.5 Hz, H-3), 2.56 (ddd, 1H, J=1.8, 8.0, 14.5 Hz, H-3); IR (KBr): 1699 cm^{-1}; Anal. Calcd for $C_{24}H_{17}NO_2F_6$: C, 61.94; H, 3.68; N, 3.01 ; F, 24.49. Found: C, 62.22; H, 3.62; N, 2.96; F, 24.41.

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