

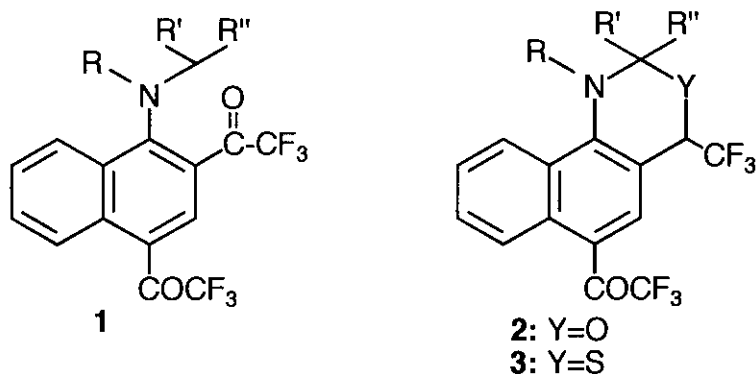
A CONVENIENT SYNTHESIS OF FLUORINE-CONTAINING 2,5-EPOXYNAPHTH[1,2-*b*]AZEPINES BY THERMALLY INDUCED CYCLIZATION OF *N*-ALLYL SUBSTITUTED 2,4-BIS(TRIFLUOROACETYL)-1-NAPHTHYLAMINES

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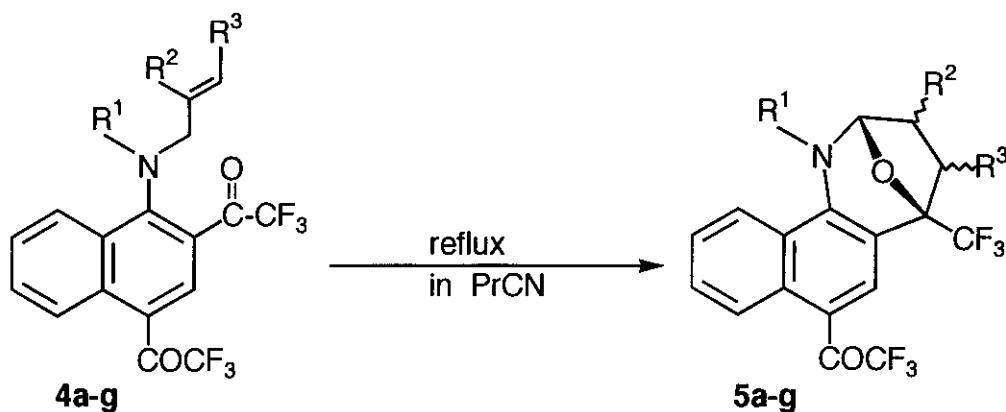
Abstract - Thermally induced cyclization of *N*-allyl substituted 2,4-bis-(trifluoroacetyl)-1-naphthylamines (**4**) proceeded easily in refluxing butyronitrile to give the corresponding 7-trifluoroacetyl-5-trifluoromethyl-2,5-epoxynaphth-[1,2-*b*]azepines (**5**) in excellent yields.

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 substitutions³ and their synthetic applications⁴ 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-



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



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)}

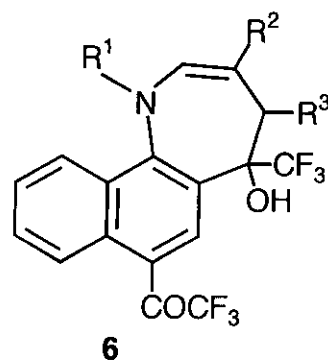
Entry	Substrate	Time(h)	Product	Yield ^{b)} (%)	endo : exo ^{c)}
1	4a	24	5a	100	—
2	4b	24	5b	100	—
3	4c	72	5c	83	—
4	4d	24	5d	100	55 : 45
5	4e	24 ^{d)}	5e	86	60 : 40
6	4f	24	5f	22 ^{e)}	0 : 100
7	4g	24	5g	70 ^{f)}	0 : 100

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 ¹H-NMR (250 MHz) analysis. d) Mesitylene was used as a solvent instead of butyronitrile. e) With 67 wt% yield of unknown 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**).

The structures of compounds (**5a-g**) were determined on the basis of their ¹H-NMR and IR spectra, together with elemental analyses. As a representative case, **5b** was further confirmed by ¹³C-NMR spectral data.⁸ ¹³C-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. $^1\text{H-NMR}$ spectra provided diagnostic information for the assignment of stereochemistry. In $^1\text{H-NMR}$ spectra of **5d** and **5e**, the bridgehead H-2 of *endo*-isomer appears as doublet with large vicinal H₂-H₃ 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_E3-5 was observed for C_H3-4 of *exo*-**5f**. Moreover, stereochemical configuration of *exo*-**5g** was determined by judging from its vicinal H₂-H₃ and H₃-H₄ 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.

ACKNOWLEDGEMENTS

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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 °C; ¹H-NMR (δ, 250 MHz, CDCl₃): 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, CH₃), 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 C₁₈H₁₃NO₂F₆: 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 °C; ¹H-NMR (δ, 60 MHz, CDCl₃): 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, NCH₂), 2.73-1.73 (m, 4H, H-3, -4), 1.39 (t, 3H, J=7 Hz, CH₃); ¹³C-NMR (δ, CDCl₃): 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 C₁₉H₁₅NO₂F₆: 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 °C; ¹H-NMR (δ, 60 MHz, CD₃CN): 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 C₁₇H₁₁NO₂F₆: 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 °C; ¹H-NMR (δ, 250 MHz, CDCl₃): 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, NCH₃), 3.21 (s, 1.35H, NCH₃), 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, CH₃-3), 1.00 (d, 1.65H, $J=7.2$ Hz, CH₃-3); IR (KBr): 1691 cm⁻¹; Anal. Calcd for C₁₉H₁₅NO₂F₆: 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 °C; ¹H-NMR (δ, 250 MHz, CDCl₃): 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, NCH₃), 3.27 (s, 1.2H, NCH₃), 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 C₁₈H₁₂NO₂ClF₆: 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 °C/5 mmHg (oven temperature); ¹H-NMR (δ, 250 MHz, CDCl₃): 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, NCH₃), 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, CH₃-4); IR (film): 1698 cm⁻¹; Anal. Calcd for C₁₉H₁₅NO₂F₆: 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 °C; ¹H-NMR (δ, 250 MHz, CDCl₃): 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, C₆H₅), 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, CH₃), 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 C₂₄H₁₇NO₂F₆: 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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