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

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Abstract - Thermally induced cyclization of \textit{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-\textit{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.\textsuperscript{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.\textsuperscript{2} Furthermore, in the course of our ongoing investigations on novel aromatic nucleophilic substitutions\textsuperscript{3} and their synthetic applications\textsuperscript{4} to the construction of various naphthalene-fused heterocycles bearing trifluoromethyl groups, we have recently reported that \textit{N},\textit{N}-dialkyl-2,4-bis(trifluoroacetyl)-1-naphthylamines (1) undergo novel cyclizations to give the corresponding fluorine-containing naphth[1,2-\textit{d}][1,3]oxazines (2)\textsuperscript{5} and naphth[1,2-\textit{d}][1,3]thiazines (3)\textsuperscript{6} in high yields. In connection with these works, we now communicate thermally induced cyclization of \textit{N}-allyl substituted 2,4-bis(trifluoroacetyl)-1-naphthylamines (4), in which the products were not expected naphth[1,2-
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
<table>
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<td>70f)</td>
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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 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 $^1$H-NMR and IR spectra, together with elemental analyses. As a representative case, 5b was further confirmed by $^{13}$C-NMR spectral data. $^{13}$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. 1H-NMR spectra provided diagnostic information for the assignment of stereochemistry. In 1H-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 CF3-5 was observed for CH3-4 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

A financial support by a Grant-in-Aid for Scientific Research (No. 07651058) from the Ministry of Education, Science, and Culture, Japan is gratefully acknowledged.

REFERENCES


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. 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.

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), 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 or -4). IR (KBr): 1704 cm⁻¹; Anal. Calcd for C_{18}H_{15}NO₅F₆: 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), 128.7 (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_{18}H_{13}NO₂F₆: 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), 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}NO₂F₆: 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, NCH$_3$), 3.21 (s, 1.35H, NCH$_3$), 2.97-2.78 (m, 0.55H, H-9, -10), 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$_{15}$NOZF$_6$: 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 °C; $^1$H-NMR (δ, 250 MHz, CDC$_3$): 9.00-8.93 (m, 1H, H-8), 8.26-8.13 (m, 2H, H-6, -11), 7.72-7.57 (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$_2$ClF$_6$: 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 °C/5 mmHg (oven temperature); $^1$H-NMR (δ, 250 MHz, CDC$_3$): 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$_2$F$_6$: C, 56.58; H, 3.75; N, 3.47; F, 26.90. Found: C, 56.68; H, 3.65; N, 3.46; F, 28.13. 5g (exo): mp 160-161 °C; $^1$H-NMR (δ, 250 MHz, CDC$_3$): 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$_6$H$_5$), 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 (dd, 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$_2$F$_6$: 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.

Received, 2nd May, 1997