A FACILE AND CONVENIENT SYNTHETIC METHOD FOR FLUORINE-CONTAINING NAPHTHO[1,2-*e*][1,4]DIAZEPINES, NAPHTHO[1,2-*e*][1,4]DITHIEPINS AND NAPHTHO[1,2-*e*]-[1,4]DIOXEPINS

Etsuji Okada,* Norikado Tsukushi, Nobukazu Kunihiro, and Yoshitsugu Tomo

Department of Chemical Science and Engineering, Faculty of Engineering, Kobe University, Kobe 657-8501, Japan

Abstract - *N*,*N*-Dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**) reacted cleanly with 1,2-diamines, 1,2-ethanedithiol, and ethylene glycol to afford the corresponding naphtho[1,2-*e*][1,4]diazepines (**2**-**4**), naphtho[1,2-*e*][1,4]dithiepins (**5**), and naphtho[1,2-*e*][1,4]dioxepins (**6**), respectively, in excellent yields.

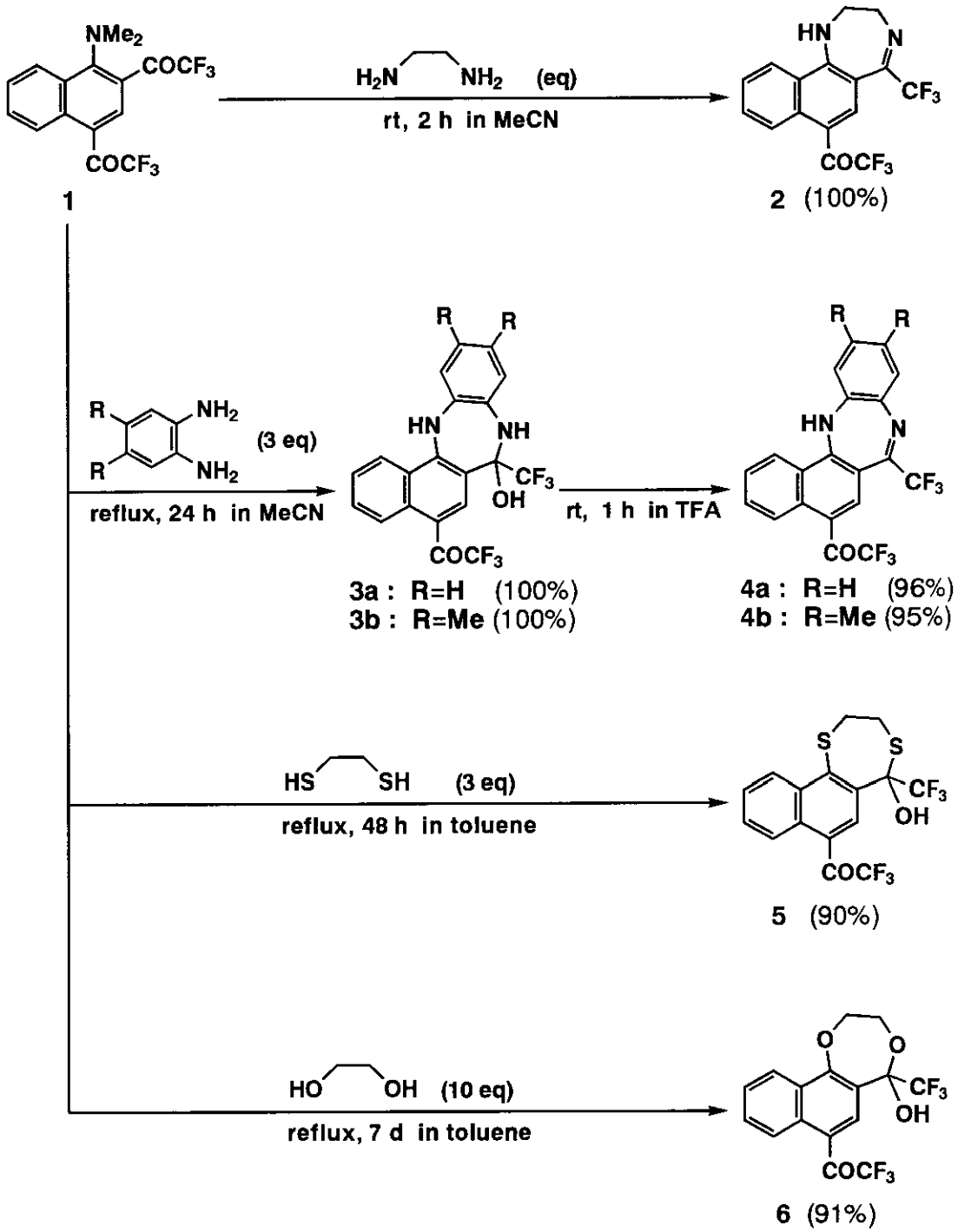
1,4-Diazepine and the related derivatives constitute an important class of heterocyclic compounds and many thousands of them have been synthesized as potential drugs.[1] Besides, considerable attention in recent years has been paid to the development of new methodologies for the synthesis of various fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing interesting biological activities for their potential use in medicinal and agricultural scientific fields.[2] Previously we reported that *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**) undergoes a novel aromatic nucleophilic substitution with various amines, thiols, and alcohols to give the corresponding 2,4-bis(trifluoroacetyl)-1-naphthylamines, sulfides, and ethers in excellent yields.[3] Later, we succeeded in applying this type of aromatic nucleophilic substitution to the syntheses of naphthalene-fused heterocycles bearing trifluoromethyl groups.[4] In connection with these works, we now wish to report here the

syntheses of fluorine-containing naphthalene-fused diazepines, dithiepins, and dioxepins, which are expected to exhibit peculiar bioactivities, by N-N, N-S, and N-O exchange reactions of **1** with 1,2-diamines, 1,2-ethanedithiol, and ethylene glycol and subsequent cyclization.

Reaction of **1**[3a] with 1,2-ethylenediamine proceeded easily at room temperature to give the desired 7-trifluoroacetyl-5-trifluoromethyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,4]diazepine (**2**) quantitatively without being accompanied by intermediary cyclic hemiaminal, 7-trifluoroacetyl-5-trifluoromethyl-5-hydroxy-2,3,4,5-tetrahydro-1*H*-naphtho[1,2-*e*][1,4]diazepine (Scheme 1). In contrast to this, while the reactions of **1** with such aromatic diamines as 1,2-phenylenediamine and its 4,5-dimethyl-substituted derivative were performed under forced conditions (for 24 h in refluxing MeCN), the relatively stable hemiaminals (**3a**,**b**) were produced in quantitative yields and could easily be isolated by column chromatography on silica gel. Treatment of **3a**,**b** with trifluoroacetic acid at room temperature for 1 h caused dehydration to provide naphthodiazepines (**4a**,**b**) in more than 95% yield. Next, we examined the reaction of **1** with 1,2-ethanedithiol in order to synthesize fluorine-containing naphthalene-fused dithiepin derivative and found it occurred readily in refluxing toluene for 48 h to afford 7-trifluoroacetyl-5-trifluoro-methyl-5-hydroxy-2,3-dihydro-5*H*-naphtho[1,2-*e*][1,4]dithiepin (**5**) in 90% yield. Further, the present reaction was applicable to ethylene glycol and the target compound, naphtho[1,2-*e*][1,4]dioxepin (**6**) was cleanly obtained in 91% yield without any formation of decomposition products.

The structures of all new compounds (**2**-**6**) were determined on the basis of their ^{1}H-NMR and IR spectra, together with elemental analyses. Those of dihydrodiazepines (**2** and **3**), dihydrodithiepins (**5**), and dihydrodioxepins (**6**) were further confirmed by ^{13}C-NMR spectral data. In especial, ^{13}C-NMR spectra of **3**, **5**, and **6** showed characteristic signals for the hemiaminal, monothiohemiacetal, and hemiacetal sp^3-carbons bearing CF_3 group at δ = 84.9 - 99.8 (q, J_{CF} = 28.1 - 33.0 Hz), respectively. This presented unambiguous evidence supporting the corresponding heterocyclic ring formation. Moreover, in the ^{13}C-NMR spectrum of **2**, there appeared one diagnostic signal for the imine sp^2-carbon in the dihydrodiazepine ring, being linked to CF_3 group, at δ = 156.6 (q, J_{CF} = 30.5 Hz).

Thus, the present method provides a simple and efficient access to CF_3-containing naphtho[1,2-*e*]-


NMe2
COCF3
COCF3
1
H2N NH2 (eq)
rt, 2 h in MeCN
HN
N
CF3
COCF3
2 (100%)
R
NH2
(3 eq)
reflux, 24 h in MeCN
HN
NH
CF3
OH
COCF3
3a : R=H (100%)
3b : R=Me (100%)
rt, 1 h in TFA
4a : R=H (96%)
4b : R=Me (95%)
HS SH (3 eq)
reflux, 48 h in toluene
S
CF3
OH
5 (90%)
HO OH (10 eq)
reflux, 7 d in toluene
O
6 (91%)

Scheme 1

[1,4]diazepines, -dithiepins, and -dioxepins, which are not easily obtained by other methods. Further investigations on this type of heterocyclic ring forming reaction of **1** with various *unsymmetrical* bifunctional nucleophiles ($HYCH_2CH_2ZH$, Y ≠ Z: NH, S, O) such as 2-aminoethanethiols, 2-aminoethanols, and 2-mercaptoethanols, as an extension of the present *symmetrical* bifunctional ones ($HYCH_2CH_2YH$, Y: NH, S, O), are currently under way and the results will be published in our forthcoming papers.

EXPERIMENTAL

All melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi EPI-G3 spectrophotometer. ^1H- and ^{13}C-NMR spectra were obtained with JEOL PMX 60SI and FX 90Q instruments 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 a silica gel column (Wakogel C-200; 100-200 mesh). All reagents were obtained commercially and used without further purification. Final purification of all products for elemental analyses was done by recrystallization.

Reaction of *N,N*-Dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (1) with 1,2-Diamines;

***with 1,2-Ethylenediamine*:** To a solution of **1**[3a] (363 mg, 1 mmol) in MeCN (8 mL) was added 1,2-ethylenediamine (60 mg, 1 mmol) and the mixture was stirred at rt for 2 h. After removal of the solvent under reduced pressure the crude product was chromatographed using benzene/EtOAc (19:1) as eluent to give **2** (360 mg, 100%): mp 173-174 ℃ ($CHCl_3$/EtOAc); IR (KBr) 3350, 3275, 3125, 1670, 1645, 1615, 1595, 1557, 1508 cm^{-1}; ^1H-NMR ($CDCl_3/CD_3CN$) 9.07-8.90 (m, 1H, H-8), 8.28 (br s, 1H, H-6), 7.99-7.32 (m, 3H, H-9, -10, -11), 7.43-6.77 (br, 1H, NH), 4.37-4.02 (br, 2H, H-3), 3.88-3.68 (m, 2H, H-2); ^{13}C-NMR (CD_3SOCD_3) 177.0 (q, J_{CF}=31.7), 156.6 (q, J_{CF}≈30.5), 151.4 (s), 137.2 (d), 132.2 (s), 131.0 (d), 126.7 (d), 125.4 (d), 124.2 (s), 123.3 (d), 120.7 (q, J_{CF}=279.6), 117.4 (q, J_{CF}=291.8), 110.9 (s),

103.2 (s), 52.9 (t), 48.4 (t). Anal. Calcd for $C_{16}H_{10}N_2OF_6$: C, 53.34; H, 2.80; N, 7.78; F, 31.64. Found: C, 53.23; H, 2.74; N, 7.70; F, 31.32.

***with 1,2-Phenylenediamines*; General Procedure:** To a solution of **1** (363 mg, 1 mmol) in MeCN (8 mL) was added appropriate 1,2-phenylenediamine (3 mmol) and the mixture was stirred at 82 ℃ (reflux) for 24 h. The solvent was evaporated under reduced pressure, and CH_2Cl_2 (50 mL) was added to the residue. The solution was washed with 1N HCl (100 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the crude product was chromatographed using benzene/EtOAc (19:1) for **3a** and **3b** as eluent.

3a: yield 100%; mp 172-173 ℃ ($CHCl_3$/EtOAc); IR (KBr) 3430, 3300, 1665, 1605, 1566, 1542, 1513 cm^{-1}; ^{1}H-NMR (CD_3CN/$CDCl_3$) 9.07-8.90 (m, 1H), 8.55 (br s, 1H), 8.07-7.85 (br m, 2H), 7.64-7.40 (m, 2H), 7.12-6.80 (m, 4H), 5.36 (br s, 1H), 4.80 (br s, 1H); ^{13}C-NMR (CD_3SOCD_3) 178.0 (q, J_{CF}=31.7), 145.2 (s), 138.7 (d), 134.1 (s), 133.1 (s), 131.4 (s), 130.5 (d), 126.7 (d), 125.6 (d), 124.8 (q, J_{CF}=293.0), 124.8 (s), 124.4 (d), 124.0 (d), 122.2 (d), 121.7 (d), 121.5 (d), 117.9 (q, J_{CF}=293.0), 114.1 (s), 113.0 (s), 85.2 (q, J_{CF}=28.1). Anal. Calcd for $C_{20}H_{12}N_2O_2F_6$: C, 56.35; H, 2.84, N, 6.57. Found: C, 56.62; H, 3.02; N, 6.54.

3b: yield 100%; mp 201-202 ℃ (hexane/EtOAc); IR (KBr) 3440, 3350, 1660, 1598, 1565, 1540, 1512 cm^{-1}; ^{1}H-NMR ($CDCl_3$/CD_3CN) 9.19-9.03 (m, 1H), 8.63 (br s, 1H), 8.30-8.06 (m, 2H), 7.76-7.41 (m, 2H), 6.92 (s, 1H), 6.69 (s, 1H), 5.68 (s, 1H), 4.95 (s, 1H), 2.15 (s, 6H); ^{13}C-NMR (CD_3SOCD_3) 177.3 (q, J_{CF}=30.5), 145.0 (s), 138.6 (d), 132.7 (s), 132.1 (s), 131.5 (s), 130.3 (d), 129.5 (s), 128.4 (s), 126.4 (d), 125.1 (d), 124.5 (q, J_{CF}=293.0), 124.3 (s), 123.8 (d), 122.2 (d), 122.1 (d), 117.6 (q, J_{CF}=294.2), 113.5 (s), 111.9 (s), 84.9 (q, J_{CF}=28.1), 18.8 (q), 18.6 (q). Anal. Calcd for $C_{22}H_{16}N_2O_2F_6$: C, 58.16; H, 3.55, N, 6.17. Found: C, 58.07; H, 3.82; N, 5.99.

Dehydration of Dihydronaphthodiazepines (3a, b); General Procedure: A solution of dihydronaphthodiazepines (**3a, b**; 1 mmol) and TFA (5 mL) was stirred at rt for 1 h, the solvent was removed under reduced pressure, and CH_2Cl_2 (50 mL) was added to the residue. The solution was washed

with saturated Na_2CO_3 (100 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the crude product was chromatographed using hexane/benzene (2:3) for **4a, b** as eluent.

4a: yield 96%; mp 217-218 ℃ ($CHCl_3$/EtOAc); IR (KBr) 3415, 1690, 1645, 1615, 1561, 1511 cm^{-1}; ^{1}H-NMR (CD_3CN) 8.91-8.69 (m, 1H), 8.40-8.11 (m, 2H), 7.90-7.65 (m, 2H), 7.40-6.89 (m, 4H), 2.11 (s, 1H). Anal. Calcd for $C_{20}H_{10}N_2OF_6$: C, 58.83; H, 2.47; N, 6.86; F, 27.92. Found: C, 58.55; H, 2.40; N, 7.04; F, 27.81.

4b: yield 95%; mp 245-246 ℃ ($CHCl_3$/EtOAc); IR (KBr) 3415, 1695, 1630, 1618, 1597, 1565, 1504 cm^{-1}; ^{1}H-NMR (CD_3CN/CD_3SOCD_3) 8.87-8.51 (m, 2H), 8.14 (s, 1H), 8.01 (s, 1H), 7.87-7.52 (m, 2H), 6.90 (s, 1H), 6.84 (s, 1H), 2.15 (s, 6H). Anal. Calcd for $C_{22}H_{14}N_2OF_6$: C, 60.56; H, 3.23; N, 6.42. Found: C, 60.39; H, 3.06; N, 6.47.

Reaction of 1 with 1,2-Ethanedithiol: To a solution of **1** (363 mg, 1 mmol) in toluene (8 mL) was added 1,2-ethanedithiol (283 mg, 3 mmol) and the mixture was stirred at 111 ℃ (reflux) for 48 h. The solvent was removed under reduced pressure and the crude product was chromatographed using hexane/benzene (2:3) as eluent to give **5** (371 mg, 90%): mp 100-101 ℃ (hexane/$CHCl_3$); IR (KBr) 3350, 1728, 1590, 1545, 1510 cm^{-1}; ^{1}H-NMR 9.20-8.91 (m, 1H, H-8), 8.86-8.59 (m, 1H, H-11), 8.45 (br s, 1H, H-6), 8.04-7.68 (m, 2H, H-9, -10), 6.17 (br, 1H, OH), 3.37-2.25 (m, 4H, H-2, -3); ^{13}C-NMR 182.5 (q, J_{CF}=34.2), 137.3 (s), 136.7 (d), 131.6 (s), 130.7 (d), 129.5 (s), 129.0 (d), 127.6 (s), 127.4 (d), 126.1 (s), 125.3 (d), 124.8 (q, J_{CF}=285.7), 116.6 (q, J_{CF}=291.8), 87.9 (q, J_{CF}=29.3), 34.5 (t), 31.4 (t). Anal. Calcd for $C_{16}H_{10}O_2F_6S_2$: C, 46.60; H, 2.44; F, 27.64. Found: C, 46.32; H, 2.44; F, 27.52.

Reaction of 1 with Ethylene Glycol: To a solution of **1** (363 mg, 1 mmol) in toluene (8 mL) was added ethylene glycol (621 mg, 10 mmol) and the mixture was stirred at 111 ℃ (reflux) for 7 d. The solvent was removed under reduced pressure, and CH_2Cl_2 (50 mL) was added to the residue. The solution was washed with H_2O (100 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the crude product was chromatographed using benzene as eluent to give **6** (346 mg, 91%): mp 165-166 ℃ ($CHCl_3$/EtOAc); IR (KBr) 3450, 1705, 1620, 1573, 1512 cm^{-1}; ^{1}H-NMR ($CDCl_3/CD_3CN$) 8.86-8.63 (m, 1H, H-

8), 8.43-8.20 (m, 2H, H-6, -11), 7.83-7.40 (m, 2H, H-9, -10), 5.96-5.26 (br, 1H, OH), 5.03-3.83 (m, 4H, H-2, -3); ^{13}C-NMR (CD_3COCD_3) 181.2 (q, J_{CF}=33.0), 157.9 (s), 135.9 (d), 134.4 (s), 131.5 (d), 129.9 (s), 128.2 (d), 125.7 (d), 124.4 (d), 123.7 (q, J_{CF}=288.1), 121.9 (s), 120.8 (s), 117.7 (q, J_{CF}=293.0), 99.8 (q, J_{CF}=33.0), 73.5 (t), 61.5 (t). Anal. Calcd for $C_{16}H_{10}O_4F_6$: C, 50.54; H, 2.65; F, 29.98. Found: C, 50.46; H, 2.48; F, 29.88.

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