A FACILE AND CONVENIENT SYNTHETIC METHOD FOR FLUORINE-CONTAINING 1,2-DIHYDROBENZO[h]QUINAZOLINES AND BENZO[h]QUINAZOLINES

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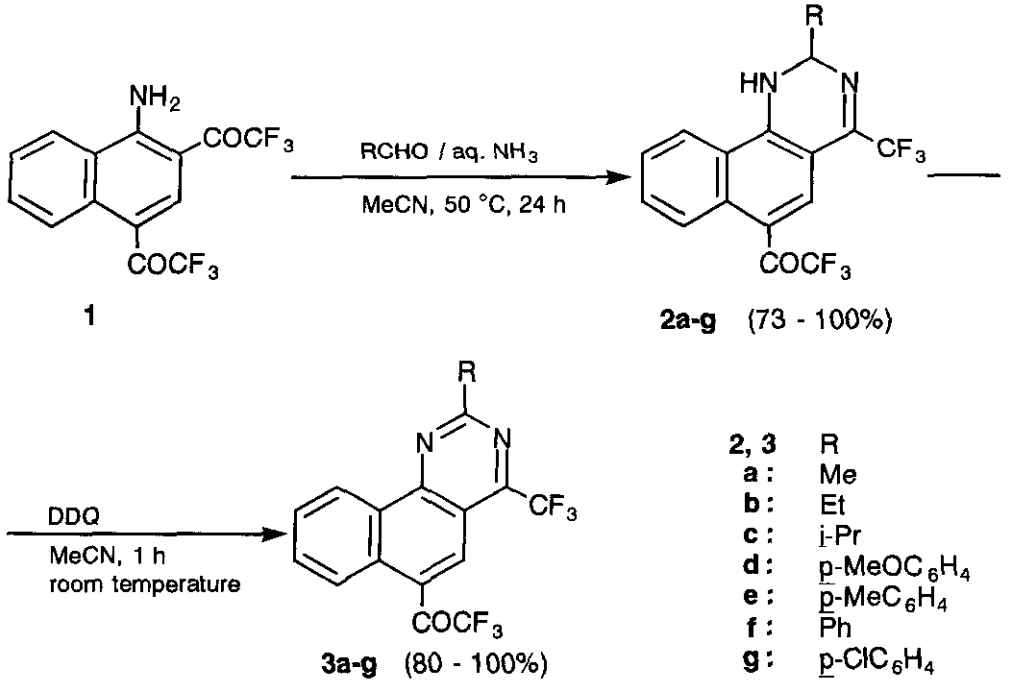
Abstract - 2,4-Bis(trifluoroacetyl)-1-naphthylamine (1) reacted easily with various aldehydes in the presence of aqueous ammonia under mild conditions to afford 6-trifluoroacetyl-4-trifluoromethyl-1,2-dihydrobenzo[h]quinazolines (2) in excellent yields. Dehydrogenation of 2 with DDQ gave the corresponding benzo[h]quinazolines (3) in high yields.

Benzo[h]quinazoline and its derivatives are important heterocyclic systems, constituting the structure of many naturally occurring products and having interesting pharmacological properties as antitumor and antidepressive agents.[1-3] Besides, recently the development of new methodologies for the synthesis of various fluorine-containing heterocycles has received an increasing interest, since many kinds of these compounds are now widely recognized as important organic materials showing interesting biological activities for their potential use in medicinal and agricultural scientific fields.[4-6] Previously we reported that N,N-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine undergoes a novel aromatic nucleophilic substitution with various amines,[7,9,10] thiols,[8,10] and alcohols[8,10] to give the corresponding 2,4-bis(trifluoroacetyl)-1-naphthylamines, sulfides, and ethers in excellent yields. Later, we succeeded in applying this type of aromatic nucleophilic substitution and the related reactions to the syntheses of naphthalene-fused

heterocycles bearing trifluoromethyl groups, such as benzindoles,[11] benzindazoles,[12] naphthisoxazoles,[12] benzacridines,[13] naphthothiophenes,[14] benzothioxanthenes,[15] benzoxanthenes,[15] naphthoxazines,[16,17] and naphthothiazines.[18] In connection with these works, we attempted to utilize 2,4-bis(trifluoroacetyl)-1-naphthylamine (1) as a new building block for construction of fluorine-containing heterocyclic compounds and found that the captioned compounds (2 and 3) can be easily synthesized by the reaction of 1 with aldehydes in the presence of aqueous ammonia.



1

2a-g (73 - 100%)

3a-g (80 - 100%)

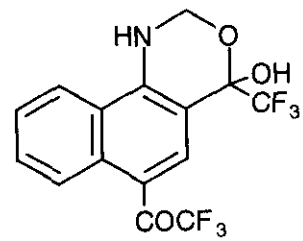
2, 3	R
a :	Me
b :	Et
c :	i-Pr
d :	p-$MeOC_6H_4$
e :	p-MeC_6H_4
f :	Ph
g :	p-ClC_6H_4

Scheme 1

2-Alkyl-6-trifluoroacetyl-4-trifluoromethyl-1,2-dihydrobenzo[h]quinazolines (**2a-c**) were readily obtained in 73-97% yields by the reaction of **1**[7] with aliphatic aldehydes, such as acet-, propion-, and isobutyraldehydes in the presence of aqueous ammonia at 50 °C for 24 h (Scheme 1). Similarly, such aromatic aldehydes as p-substituted benzaldehydes reacted with **1** and aqueous ammonia under mild conditions to afford the corresponding 2-aryl-1,2-dihydrobenzo[h]quinazolines (**2d-g**) in 73-100% yields. In the cases of benz-

and p-chlorobenzaldehydes, dehydrogenated products of **2f** and **2g**, benzo[h]quinazolines (**3f** and **3g**) were also formed as minor products in 27% and 18% yields, respectively. Treatment of 1,2-dihydrobenzo[h]quinazolines (**2a-g**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at room temperature for 1 h caused smooth dehydrogenation to give the desired benzo[h]quinazolines (**3a-g**) in 80-100% yields.

In contrast to the results mentioned above, there was no incorporation of the nitrogen atom of ammonia into products in the reaction of **1** with formaldehyde (formalin) and fluorine-containing 1,4-dihydro-2H-naphth[1,2-d][1,3]oxazine (**4**) was solely obtained in 98% yield without any formation of the corresponding 1,2-dihydrobenzo[h]quinazoline (**2**: R=H).



4

The structures of all new compounds (**2-4**) were determined from their ^{1}H-nmr and ir spectra, together with elemental analyses.

In conclusion, the present method provides a facile and convenient access to CF_3-containing naphthalene-fused pyrimidines (benzoquinazolines) which are not easily obtained by other methods. Further utilization of **1** as a useful synthetic intermediate for the preparation of various fluorine-containing heterocycles which are potentially medicinally active are now under investigation and will be presented elsewhere. Evaluation of biological activities for **2-4** is also in progress.

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 reagents were

obtained commercially and used without further purification. Final purification of all products for elemental analyses was done by recrystallization.

Reaction of 2,4-Bis(trifluoroacetyl)-1-naphthylamine (1) with Aldehydes in the Presence of Ammonia; General Procedure: To a solution of **1**[7] (335 mg, 1 mmol) in MeCN (5 ml) were added the appropriate aldehyde (3 mmol) and aqueous ammonia (28 wt.%, 183 mg, 3 mmol). The mixture was stirred at 50 °C for 24 h, the solvent was removed under reduced pressure, and CH_2Cl_2 (50 ml) was added to the residue. This solution was washed with H_2O (100 ml) and dried (Na_2SO_4). The solvent was evaporated and the crude product was chromatographed using benzene/EtOAc (7:3) for **2a** and **4**, benzene/EtOAc (9:1) for **2b-d** and **2g**, hexane/benzene (3:7) for **2e**, and benzene for **2f** as eluent.

In the synthesis of **2d**, **2e**, and **4**, 5 mmol of aldehyde and 3 mmol of ammonia were used to 1 mmol of **1**. The reaction with p-anisaldehyde was carried out at room temperature. In the reactions with benz- and p-chlorobenzaldehydes, **3f** and **3g** were formed as by-products in 27% and 18% yields, respectively, and both separated from major components (**2f** and **2g**) by chromatography using hexane/benzene (1:1).

2a: yield 97%; mp 190-191 °C ($CHCl_3$/EtOAc); ir (KBr) 3348, 1641, 1619 cm^{-1}; ^{1}H-nmr (CD_3CN/$CDCl_3$) 8.96 (dd, 1H, J=2, 7, H-7), 8.10 (br s, 1H, H-5), 7.92-7.37 (m, 3H, H-8, -9, -10), 6.87-6.40 (br, 1H, NH), 5.56 (q, 1H, J=7, H-2), 1.65 (d, 3H, J=7, CH_3). Anal. Calcd for $C_{16}H_{10}N_2OF_6$: C, 53.34; H, 2.80; N, 7.78. Found: C, 52.85; H, 2.77; N, 7.91.

2b: yield 73%; mp 165-166 °C ($CHCl_3$/EtOAc); ir (KBr) 3335, 1641, 1617 cm^{-1}; ^{1}H-nmr (CD_3CN/$CDCl_3$) 9.05-8.90 (m, 1H, H-7), 8.12 (s, 1H, H-5), 7.97-7.30 (m, 3H, H-8, -9, -10), 6.80-6.50 (br, 1H, NH), 5.46 (br t, 1H, J=5, H-2), 2.10-1.74 (m, 2H, CH_2), 1.07 (t, 3H, J=7, CH_3). Anal. Calcd for $C_{17}H_{12}N_2OF_6$: C, 54.55; H, 3.23; N, 7.49; F, 30.45. Found: C, 54.25; H, 3.12; N, 7.47; F, 30.19.

2c: yield 95%; mp 121-122 °C (hexane/$CHCl_3$); ir (KBr) 3343, 1643, 1614 cm^{-1}; ^{1}H-nmr 9.25-9.10 (m, 1H, H-7), 8.33 (br s, 1H, H-5), 7.93-7.42 (m, 3H, H-8, -9, -10), 5.70 (br s, 1H, NH), 5.43 (d, 1H, J=5, H-2), 2.20 (double heptuplet, 1H, J=5, 7, C<u>H</u>Me_2), 1.26 (d, 6H, J=7, CH_3). Anal. Calcd for $C_{18}H_{14}N_2OF_6$: C, 55.68; H, 3.63; N, 7.21. Found: C, 55.26; H, 3.51; N, 7.07.

2d: yield 95%; mp 140-141 °C ($CHCl_3$); ir (KBr) 3360, 1691, 1647, 1616 cm $^{-1}$; ^{1}H-nmr 9.08-8.91 (m, 1H, H-7), 8.25 (br s, 1H, H-5), 7.77-7.23 (m, 5H, H-8, -9, -10, p-$MeOC_6\underline{H}_4$), 6.76 (d, 2H, J=5, p-$MeOC_6\underline{H}_4$), 6.29 (s, 1H, H-2), 5.98-5.66 (br, 1H, NH), 3.70 (s, 3H, OCH_3). Anal. Calcd for $C_{22}H_{14}N_2O_2F_6$: C, 58.41; H, 3.12; N, 6.19. Found: C, 57.95; H, 3.17; N, 6.19.

2e: yield 100%; mp 138-139 °C (hexane/$CHCl_3$); ir (KBr) 3387, 1692, 1649, 1616 cm^{-1}; ^{1}H-nmr 9.16-8.97 (m, 1H, H-7), 8.32 (br s, 1H, H-5), 7.84-7.03 (m, 7H, H-8, -9, -10, p-$MeC_6\underline{H}_4$), 6.36 (br s, 1H, H-2), 6.15-5.85 (br, 1H, NH), 2.29 (s, 3H, CH_3). Anal. Calcd for $C_{22}H_{14}N_2OF_6$: C, 60.56; H, 3.23; N, 6.42. Found: C, 60.00; H, 3.04; N, 6.37.

2f: yield 73%; mp 149-150 °C (hexane/$CHCl_3$); ir (KBr) 3362, 1686, 1646, 1616 cm^{-1}; ^{1}H-nmr 9.00-8.86 (m, 1H, H-7), 8.19 (br s, 1H, H-5), 7.74-7.17 (m, 8H, H-8, -9, -10, C_6H_5), 6.29 (br s, 1H, H-2), 6.19-5.89 (br, 1H, NH). Anal. Calcd for $C_{21}H_{12}N_2OF_6$: C, 59.72; H, 2.86; N, 6.63. Found: C, 59.47; H, 2.60; N, 6.76.

2g: yield 77%; mp 157-158 °C ($CHCl_3$); ir (KBr) 3405, 1650, 1613 cm^{-1}; ^{1}H-nmr ($CD_3CN/CDCl_3$) 9.05-8.89 (m, 1H, H-7), 8.19 (br s, 1H, H-5), 7.99-7.08 (m, 7H, H-8, -9, -10, p-$ClC_6\underline{H}_4$), 6.51 (br s, 1H, H-2), 2.73-2.05 (br, 1H, NH). Anal. Calcd for $C_{21}H_{11}N_2OClF_6$: C, 55.22; H, 2.43; N, 6.13. Found: C, 55.08; H, 2.32; N, 6.08.

4: yield 98%; mp 138-139 °C ($CHCl_3$/EtOAc); ir (KBr) 3410, 1688, 1661, 1621 cm^{-1}; ^{1}H-nmr ($CD_3CN/CDCl_3$) 9.07-8.90 (m, 1H, H-7), 8.33 (br s, 1H, H-5), 8.02-7.25 (m, 4H, H-8, -9, -10, OH), 5.94 (s, 1H, NH), 5.13 (dd, 1H, J=4, 9, H-2), 4.83 (dd, 1H, J=3, 9, H-2); ^{1}H-nmr ($CD_3CN/CDCl_3/D_2O$) 9.07-8.90 (m, 1H, H-7), 8.33 (br s, 1H, H-5), 8.02-7.25 (m, 3H, H-8, -9, -10), 5.13 (d, 1H, J=9, H-2), 4.83 (d, 1H, J=9, H-2). Anal. Calcd for $C_{15}H_9NO_3F_6$: C, 49.33; H, 2.48; N, 3.84; F, 31.20. Found: C, 49.43; H, 2.47; N, 4.13; F, 31.02.

Dehydrogenation of 1,2-Dihydrobenzo[h]quinazolines (2a-g) with DDQ; General Procedure: To a solution of **2a-g** (1 mmol) in MeCN (16 ml) was added DDQ (238 mg, 1.05 mmol) and the solution was stirred at room temperature for 1 h. The insoluble matter was separated from the solution by filtration and washed with CH_2Cl_2 (50 ml). The filtrate was washed once with 20% aq. Na_2CO_3 (100 ml), once with H_2O (100 ml), and subsequently dried

(Na_2SO_4). The solvent was evaporated to give the practically pure products (**3a-g**).

3a: yield 96%; mp 134-135 °C (hexane/benzene); ir (KBr) 1720, 1609 cm^{-1}; ^{1}H-nmr 9.30-9.17 (m, 1H, H-7), 8.57-8.40 (m, 2H, H-5, -10), 7.83-7.67 (m, 2H, H-8, -9), 3.03 (s, 3H, CH_3). Anal. Calcd for $C_{16}H_8N_2OF_6$: C, 53.64; H, 2.25; N, 7.82. Found: C, 53.52; H, 2.20; N, 7.94.

3b: yield 97%; mp 145-146 °C (hexane); ir (KBr) 1718, 1605 cm^{-1}; ^{1}H-nmr 9.34-9.12 (m, 1H, H-7), 8.55-8.39 (m, 2H, H-5, -10), 7.82-7.65 (m, 2H, H-8, -9), 3.23 (q, 2H, J=7, CH_2), 1.57 (t, 3H, J=7, CH_3). Anal. Calcd for $C_{17}H_{10}N_2OF_6$: C, 54.85; H, 2.71; N, 7.53. Found: C, 55.11; H, 2.82; N, 7.83.

3c: yield 86%; mp 129-130 °C (hexane/benzene); ir (KBr) 1723, 1605 cm^{-1}; ^{1}H-nmr 9.32-9.17 (m, 1H, H-7), 8.52-8.33 (m, 2H, H-5, -10), 7.77-7.60 (m, 2H, H-8, -9), 3.55 (heptuplet, 1H, J=7, CH), 1.57 (d, 6H, J=7, CH_3). Anal. Calcd for $C_{18}H_{12}N_2OF_6$: C, 55.97; H, 3.13; N, 7.25. Found: C, 55.72; H, 3.32; N, 7.38.

3d: yield 97%; mp 210-211 °C (benzene/EtOAc); ir (KBr) 1713, 1601 cm^{-1}; ^{1}H-nmr 9.50-9.31 (m, 1H, H-7), 8.67-8.40 (m, 4H, H-5, -10, p-$MeOC_6\underline{H}_4$), 7.86-7.72 (m, 2H, H-8, -9), 6.97 (d, 2H, J=8, p-$MeOC_6\underline{H}_4$), 3.87 (s, 3H, OCH_3). Anal. Calcd for $C_{22}H_{12}N_2O_2F_6$: C, 58.68; H, 2.69; N, 6.22. Found: C, 58.50; H, 2.51; N, 5.99.

3e: yield 100%; mp 189-190 °C (benzene/EtOAc); ir (KBr) 1715, 1606 cm^{-1}; ^{1}H-nmr 9.60-9.45 (m, 1H, H-7), 8.84-8.55 (m, 4H, H-5, -10, p-$MeC_6\underline{H}_4$), 8.12-7.82 (m, 2H, H-8, -9), 7.35 (d, 2H, J=8, p-$MeC_6\underline{H}_4$), 2.47 (s, 3H, CH_3). Anal. Calcd for $C_{22}H_{12}N_2OF_6$: C, 60.84; H, 2.78; N, 6.45. Found: C, 61.11; H, 2.78; N, 6.63.

3f: yield 80%; mp 191-192 °C (hexane/$CHCl_3$); ir (KBr) 1715, 1604 cm^{-1}; ^{1}H-nmr 9.48-9.26 (m, 1H, H-7), 8.67-8.43 (m, 4H, H-5, -10, C_6H_5), 7.92-7.38 (m, 5H, H-8, -9, C_6H_5). Anal. Calcd for $C_{21}H_{10}N_2OF_6$: C, 60.01; H, 2.40; N, 6.67; F, 27.12. Found: C, 59.49; H, 2.34; N, 6.91; F, 27.12. Found: C, 59.49; H, 2.34; N, 6.91; F, 26.92.

3g: yield 94%; mp 173-174 °C (benzene/EtOAc); ir (KBr) 1715, 1600 cm^{-1}; ^{1}H-nmr 9.32-9.16 (m, 1H, H-7), 8.52-8.37 (m, H-5, -10, p-ClC_6H_4), 7.85-7.69 (m, 2H, H-8, -9), 7.33 (d, 2H, J=9, p-ClC_6H_4). Anal. Calcd for $C_{21}H_9N_2OClF_6$: C, 55.46; H, 1.99; N, 6.16. Found: C, 55.18; H, 1.97; N, 6.22.

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