A FACILE AND CONVENIENT SYNTHETIC METHOD FOR FLUORINE-CONTAINING 1,2-DIHYDROPYRIDO-[3,2-*h*]QUINAZOLINES AND PYRIDO[3,2-*h*]QUINAZOLINES

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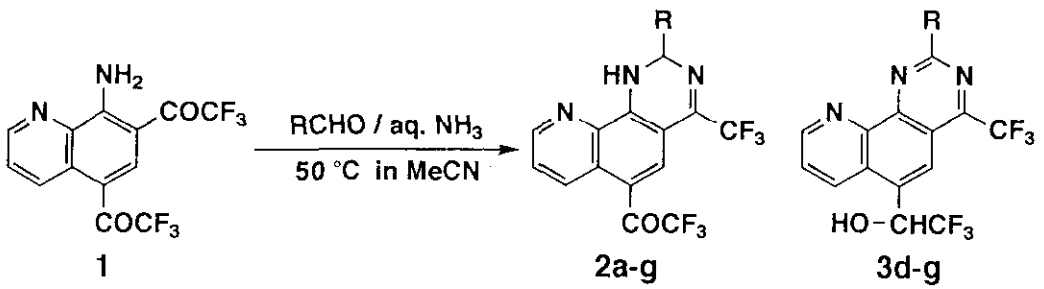
Abstract - 5,7-Bis(trifluoroacetyl)-8-quinolylamine (**1**) reacted with various aliphatic and aromatic aldehydes in the presence of aqueous ammonia to afford fluorine-containing 1,2-dihydropyrido[3,2-*h*]quinazolines (**2**) and pyrido[3,2-*h*]quinazoline-6-methanols (**3**) in moderate to high yields. Dehydrogenation of **2** with DDQ gave the corresponding pyrido-[3,2-*h*]quinazolines (**4**) in excellent yields. Conversion of alcohols (**3**) into hydrates (**4**) with DDQ was also successful.

In recent years, considerable attention has been focused on 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 showing interesting biological activities for their potential use in medicinal and agricultural scientific fields.[1] Previously we found that *N*,*N*-dimethyl-2,4-bis(trifluoro-acetyl)-1-naphthylamine undergoes a novel aromatic nucleophilic substitution with various amines, thiols and alcohols to give the corresponding N-N, N-S and N-O exchanged 2,4-bis(trifluoroacetyl)-1-naphthyl-amines, sulfides and ethers in excellent yields, respectively.[2] Up-to-dately we succeeded in extending the present S_NAr reaction to less reactive *N*,*N*-dimethyl-2-trifluoroacetyl-4-halo-1-naphthylamines.[3] Later, we carried out applying this type of aromatic nucleophilic substitution and related reactions to the simple syntheses of naphthalene-fused heterocycles bearing trifluoromethyl groups.[4] Besides, quinoline derivatives constitute an important class of heterocyclic compounds and the skeleton is found in a great

number of natural products, for example alkaloids showing interesting biological activities.[5] Therefore, we have recently reported that *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine reacts easily with various amines to give the corresponding 5,7-bis(trifluoroacetyl)-8-quinolylamines and its application to the synthesis of fluorine-containing 1*H*-pyrrolo[3,2-*h*]quinolines.[6] As a part of our systematic research program on the simple syntheses of CF_3-containing heterocycles, we attempted to utilize 5,7-bis-(trifluoroacetyl)-8-quinolylamine (**1**) as a new and convenient building block for construction of quinoline-fused heterocycles bearing trifluoromethyl group and found that the title compounds (**2** - **4**) can be very easily synthesized by the reaction of **1** with aldehydes providing the C-2 unit and ammonia used as the N-3 source of the ring. These fluorine-containing pyridoquinazolines (**2** - **4**) are expected to show interesting pharmacological properties as antifungal agents[7] and dopamine receptor agonists.[8]



1 **2a-g** **3d-g**

Scheme 1

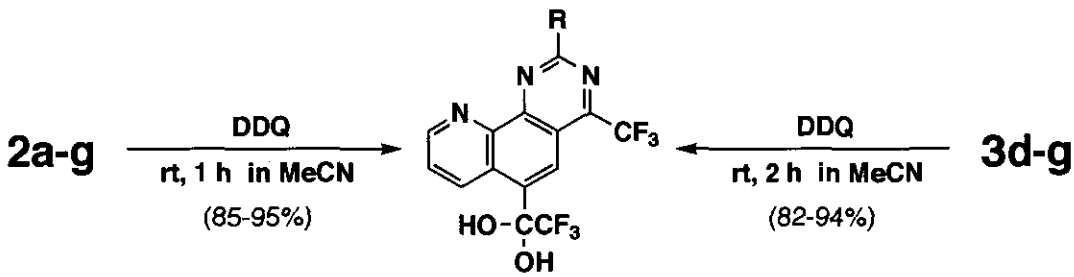
Table 1. Reaction of **1** with Aldehydes (RCHO) in the Presence of Aqueous Ammonia[a)]

Entry	R	RCHO equiv.	Time (h)	Product	Yield (%)[b)]
1	Me	3	6	**2a**	30[c)]
2	Et	3	24	**2b**	62
3	*i*-Pr	5	72	**2c**	87
4	*p*-$MeOC_6H_4$	5	24	**2d**	84 (6)
5	*p*-$MeOC_6H_4$	5	48	**2d/3d**	71/23
6	*p*-MeC_6H_4	5	24	**2e**	86 (5)
7	*p*-MeC_6H_4	5	48	**2e/3e**	71/21
8	C_6H_5	5	24	**2f**	88 (9)
9	C_6H_5	5	48	**2f/3f**	71/18
10	*p*-ClC_6H_4	5	24	**2g**	60 (39)
11	*p*-ClC_6H_4	5	96	**2g/3g**	50/46

a) Molar ratio, [**1**]/[NH_3]=1 / 3 for Entries 1 and 2; 1 / 5 for Entries 3-11. b) Isolated yields. Values in parentheses are the recovery of substrate (**1**). c) With 62 wt% yield of decomposition products.

The results are shown in Scheme 1 and summarized in Table 1. Reaction of **1**[6] with aliphatic aldehydes such as propion- and isobutyraldehydes in the presence of ammonia proceeded readily under mild conditions to afford the corresponding 2-alkyl-6-trifluoroacetyl-4-trifluoromethyl-1,2-dihydropyrido[3,2-*h*]quinazolines (**2b**, **c**) in 62-87% yields. In the case of acetaldehyde, the desired 2-methyl derivative (**2a**) was isolated in 30% yield, though accompanied by 62 wt% of decomposition products. Unfortunately, attempted reactions in order to synthesize 2-unsubstituted derivative from **1**, formaldehyde (formalin) and ammonia were unsuccessful. At 50 °C for 24 h, such aromatic aldehydes as *p*-substituted benzaldehydes reacted with **1** and aqueous ammonia to afford 2-aryl-1,2-dihydropyridoquinazolines (**2d-g**) in 60-88% yields, together with the recovery of unreacted substrate (**1**). Interestingly, in contrast to the cases of aliphatic aldehydes mentioned above, prolonged heating (48 - 96 h) for completing the reactions resulted in giving not only the *expected* **2d-g** in 50-71% yields but also the *unexpected* 2-aryl-α,4-bis(trifluoromethyl)pyrido[3,2-*h*]quinazoline-6-methanols (**3d-g**) in 18-46% yields. Separation of the **2** - **3** mixtures was easily effected by chromatography on a silica gel column.

Treatment of 1,2-dihydropyrido[3,2-*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 fluorine-containing pyrido[3,2-*h*]quinazolines (**4a-g**) in 85-95% yields (Scheme 2). 6-Trifluoroacetyl group of pyrido[3,2-*h*]-



Scheme 2

quinazolines (**4**) was found to exist as hydrate form and this phenomenon was not observed in benzo[*h*]quinazoline system.[4i] Furthermore, alcohols (**3d-g**) were also converted effectively with DDQ into **4d-g** in excellent yields.

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

Thus, the present synthetic method provides a facile and convenient access to pyrido[3,2-*h*]quinazolines

having both trifluoromethyl and trifluoroacetyl groups which are not easily obtained by other methods.

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. ^{1}H-NMR spectra were obtained with 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 taken with a Yanaco CHN Corder MT-5 analyzer. Chromatographic separations were carried out on a silica gel column (Fuji Silysia Chemical BW-127ZH; 100-270 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 5,7-Bis(trifluoroacetyl)-8-quinolylamine (1) with Aldehyde in the Presence of Ammonia; General Procedure: To a solution of **1**[6] (336 mg, 1 mmol) in MeCN (5 mL) was added the appropriate aldehyde (3 - 5 mmol) and aqueous ammonia (28 wt.%, 182 - 304 mg, 3 - 5 mmol). The mixture was stirred at 50 °C for 6 - 96 h, the solvent was removed under reduced pressure, and EtOAc (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 hexane/EtOAc (4:1) for **2a-g** and hexane/EtOAc (9:1) for **3d-g** as eluent.

2a: mp 120-121 °C (hexane); IR (KBr) 3350, 3260, 1684, 1648 cm^{-1}; ^{1}H-NMR 9.44 (dd, 1H, J=2, 9, H-7), 8.69 (dd, 1H, J=2, 4, H-9), 8.24 (br s, 1H, H-5), 7.57 (dd, 1H, J=4, 9, H-8), 7.11 (br s, 1H, NH), 5.85 (q, 1H, J=6, H-2), 1.73 (d, 3H, J=6, CH_3). Anal. Calcd for $C_{15}H_9N_3OF_6$: C, 49.87; H, 2.51; N, 11.63. Found: C, 50.06; H, 2.71; N, 11.44.

2b: mp 98-99 °C (hexane); IR (KBr) 3345, 1667, 1645 cm^{-1}; ^{1}H-NMR 9.46 (dd, 1H, J=2, 9, H-7), 8.72 (dd, 1H, J=2, 4, H-9), 8.27 (br s, 1H, H-5), 7.60 (dd, 1H, J=4, 9, H-8), 7.17 (br s, 1H, NH), 5.93-5.59 (m, 1H, H-2), 2.31-1.85 (m, 2H, CH_2), 1.37 (t, 3H, J=7, CH_3). Anal. Calcd for $C_{16}H_{11}N_3OF_6$: C, 51.21; H, 2.95; N, 11.20. Found: C, 51.28; H, 3.01; N, 11.07.

2c: mp 89-90 °C (hexane); IR (KBr) 3350, 1680, 1652 cm^{-1}; ^{1}H-NMR 9.47 (dd, 1H, J=2, 9, H-7), 8.72 (dd, 1H, J=2, 4, H-9), 8.25 (br s, 1H, H-5), 7.59 (dd, 1H, J=4, 9, H-8), 7.14 (br s, 1H, NH), 5.63 (d, 1H, J=4, H-2), 2.47-1.95 (m, 1H, CH), 1.13 (d, 6H, J=6, CH_3). Anal. Calcd for $C_{17}H_{13}N_3OF_6$: C, 52.45; H, 3.37; N, 10.79. Found: C, 52.49; H, 3.52; N, 10.60.

2d: mp 160-161 °C (hexane/EtOAc); IR (KBr) 3300, 1680, 1642 cm^{-1}; ^{1}H-NMR ($CD_3CN/CDCl_3$) 9.50 (dd, 1H, J=2, 9, H-7), 8.77 (dd, 1H, J=2, 4, H-9), 8.34 (br s, 1H, H-5), 7.92-7.32 (m, 4H, H-8, *p*-$MeOC_6\underline{H}_4$, NH), 6.94 (d, 2H, J=9, *p*-$MeOC_6\underline{H}_4$), 6.80 (br s, 1H, H-2), 3.81 (s, 3H, OCH_3). Anal. Calcd for $C_{21}H_{13}N_3O_2F_6$: C, 55.64; H, 2.89; N, 9.27. Found: C, 55.58; H, 2.90; N, 9.22.

2e: mp 149-150 °C (hexane/EtOAc); IR (KBr) 3310, 1683, 1646 cm^{-1}; ^{1}H-NMR ($CD_3CN/CDCl_3$) 9.53 (dd, 1H, J=2, 9, H-7), 8.80 (dd, 1H, J=2, 4, H-9), 8.36 (br s, 1H, H-5), 7.88-7.16 (m, 6H, H-8, *p*-$MeC_6\underline{H}_4$, NH), 6.83 (br s, 1H, H-2), 2.38 (s, 3H, CH_3). Anal. Calcd for $C_{21}H_{13}N_3OF_6$: C, 57.67; H, 3.00; N, 9.61. Found: C, 57.56; H, 2.92; N, 9.62.

2f: mp 148-149 °C (hexane/EtOAc); IR (KBr) 3370-2940, 1692, 1652 cm^{-1}; ^{1}H-NMR 9.53 (dd, 1H, J=2, 9, H-7), 8.76 (dd, 1H, J=2, 4, H-9), 8.40 (br s, 1H, H-5), 7.76-7.21 (m, 7H, H-8, C_6H_5, NH), 6.80 (br s, 1H, H-2). Anal. Calcd for $C_{20}H_{11}N_3OF_6$: C, 56.75; H, 2.62; N, 9.93. Found: C, 56.63; H, 2.74; N, 9.97.

2g: mp 172-173 °C (hexane/EtOAc); IR (KBr) 3325, 1695, 1654 cm^{-1}; ^{1}H-NMR ($CD_3CN/CDCl_3$) 9.49 (dd, 1H, J=2, 9, H-7), 8.74 (dd, 1H, J=2, 4, H-9), 8.37 (br s, 1H, H-5), 7.75-7.31 (m, 6H, H-8, *p*-$ClC_6\underline{H}_4$, NH), 6.76 (br s, 1H, H-2). Anal. Calcd for $C_{20}H_{10}N_3OClF_6$: C, 52.48; H, 2.20; N, 9.18. Found: C, 52.26; H, 2.51; N, 9.09.

3d: mp 190-191 °C (hexane/EtOAc); IR (KBr) 3385 cm^{-1}; ^{1}H-NMR 9.98-9.11 (br, 1H, OH), 9.41 (dd, 1H, J=2, 9, H-7), 8.87 (dd, 1H, J=2, 4, H-9), 8.16 (br s, 1H, H-5), 7.93 (d, 2H, J=9, *p*-$MeOC_6\underline{H}_4$), 7.65 (dd, 1H, J=4, 9, H-8), 6.99 (d, 2H, J=9, *p*-$MeOC_6\underline{H}_4$), 5.63 (q, 1H, J_{CF}=8, $CHCF_3$), 3.87 (s, 3H, OCH_3). Anal. Calcd for $C_{21}H_{13}N_3O_2F_6$: C, 55.64; H, 2.89; N, 9.27. Found: C, 55.89; H, 3.01; N, 8.90.

3e: mp 198-199 °C (hexane/EtOAc); IR (KBr) 3385 cm^{-1}; ^{1}H-NMR 9.89-9.03 (br, 1H, OH), 9.40 (dd, 1H, J=2, 9, H-7), 8.86 (dd, 1H, J=2, 4, H-9), 8.15 (br s, 1H, H-5), 7.85 (d, 2H, J=8, *p*-$MeC_6\underline{H}_4$), 7.63 (dd, 1H, J=4, 9, H-8), 7.28 (d, 2H, J=8, *p*-$MeC_6\underline{H}_4$), 5.62 (q, 1H, J_{CF}=8, $CHCF_3$), 2.43 (s, 3H, CH_3). Anal. Calcd for $C_{21}H_{13}N_3OF_6$: C, 57.67; H, 3.00; N, 9.61. Found: C, 57.70; H, 2.96; N, 9.64.

3f: mp 196-197 °C (hexane/EtOAc); IR (KBr) 3390 cm^{-1}; ^{1}H-NMR 9.88-9.31 (br, 1H, OH), 9.44 (dd, 1H, J=2, 9, H-7), 8.91 (dd, 1H, J=2, 4, H-9), 8.28-7.42 (m, 7H, H-5, H-8, C_6H_5), 5.69 (q, 1H, J_{CF}=8, $CHCF_3$). Anal. Calcd for $C_{20}H_{11}N_3OF_6$: C, 56.75; H, 2.62; N, 9.93. Found: C, 56.62; H,

2.63; N, 9.93.

3g: mp 164-165 °C (hexane/EtOAc); IR (KBr) 3365 cm^{-1}; ^{1}H-NMR 9.90-9.28 (br, 1H, OH), 9.45 (dd, 1H, J=2, 9, H-7), 8.93 (dd, 1H, J=2, 4, H-9), 8.20 (br s, 1H, H-5), 7.96 (d, 2H, J=9, *p*-$ClC_6\underline{H}_4$), 7.70 (dd, 1H, J=4, 9, H-8), 7.50 (d, 2H, J=9, *p*-$ClC_6\underline{H}_4$), 5.68 (q, 1H, J_{CF}=8, $CHCF_3$). Anal. Calcd for $C_{20}H_{10}N_3OClF_6$: C, 52.48; H, 2.20; N, 9.18. Found: C, 52.40; H, 2.58; N, 9.20.

Dehydrogenation of 1,2-Dihydropyrido[3,2-*h*]quinazolines (2a-g) and Pyrido[3,2-*h*]quinazoline-6-methanols (3d-g) with DDQ; General Procedure:

from 1,2-Dihydropyrido[3,2-h]quinazolines (2a-g) : To a solution of **2a-g** (1 mmol) in MeCN (16 mL) was added DDQ (227 mg, 1 mmol) and the solution was stirred at rt for 1 h (to **2a-g**) or 2 h (to **3d-g**). The insoluble matter was separated from the solution by filtration and washed with EtOAc (50 mL). The filtrate was washed once with saturated 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 (**4a-g**).

4a: yield 95%; mp 157 °C (decomp); IR (KBr) 3370-3110 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3) 9.60-9.15 (m, 2H, H-7, H-9), 8.79-8.39 (m, 3H, H-5, OH), 7.98 (dd, 1H, J=4, 9, H-8), 3.06 (s, 3H, CH_3). Anal. Calcd for $C_{15}H_9N_3O_2F_6$: C, 47.76; H, 2.40; N, 11.14. Found: C, 47.83; H, 2.68; N, 10.79.

4b: yield 94%; mp 168-169 °C; IR (KBr) 3330 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3) 9.50-9.13 (m, 2H, H-7, H-9), 8.73-8.34 (m, 3H, H-5, OH), 7.90 (dd, 1H, J=4, 9, H-8), 3.31 (q, 2H, J=8, CH_2), 1.50 (d, 6H, J=8, CH_3). Anal. Calcd for $C_{16}H_{11}N_3O_2F_6$: C, 49.12; H, 2.83; N, 10.74. Found: C, 48.97; H, 2.82; N, 10.45.

4c: yield 90%; mp 161-162 °C; IR (KBr) 3340 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3) 9.63-9.24 (m, 2H, H-7, H-9), 8.90-8.42 (m, 3H, H-5, OH), 8.00 (dd, 1H, J=4, 9, H-8), 3.86-3.27 (m, 1H, CH), 1.55 (d, 6H, J=7, CH_3). Anal. Calcd for $C_{17}H_{13}N_3O_2F_6$: C, 50.38; H, 3.23; N, 10.37. Found: C, 50.31; H, 3.27; N, 10.40.

4d: yield 92% (from **2d**), 94% (from **3d**); mp 218-219 °C; IR (KBr) 3360-3110 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3) 9.64-9.20 (m, 2H, H-7, H-9), 8.86-8.38 (m, 5H, H-5, *p*-$MeOC_6\underline{H}_4$, OH), 7.97 (dd, 1H, J=4, 9, H-8), 7.17 (d, 2H, J=9, *p*-$MeOC_6\underline{H}_4$), 3.90 (s, 3H, OCH_3). Anal. Calcd for $C_{21}H_{13}N_3O_3F_6$: C, 53.74; H, 2.79; N, 8.95. Found: C, 53.85; H, 3.02; N, 8.61.

4e: yield 91% (from **2e**), 90% (from **3e**); mp 200-201 °C; IR (KBr) 3360-3100 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3) 9.57-9.14 (m, 2H, H-7, H-9), 8.82-8.33 (m, 5H, H-5, *p*-$MeC_6\underline{H}_4$, OH), 7.92 (dd, 1H,

J=4, 9, H-8), 7.39 (d, 2H, J=9, *p*-$MeC_6\underline{H}_4$), 2.42 (s, 3H, CH_3). Anal. Calcd for $C_{21}H_{13}N_3O_2F_6$: C, 55.64; H, 2.89; N, 9.27. Found: C, 55.79; H, 3.15; N, 8.86.

4f: yield 89% (from **2f**), 93% (from **3f**); mp 194-195 °C; IR (KBr) 3490 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3) 9.64-9.24 (m, 2H, H-7, H-9), 8.94-8.40 (m, 5H, H-5, C_6H_5, OH), 8.15-7.48 (m, 4H, H-8, C_6H_5). Anal. Calcd for $C_{20}H_{11}N_3O_2F_6$: C, 54.68; H, 2.52; N, 9.57. Found: C, 54.54; H, 2.61; N, 9.61.

4g: yield 85% (from **2g**), 82% (from **3g**); mp 191-192 °C; IR (KBr) 3370-3100 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3) 9.68-9.25 (m, 2H, H-7, H-9), 8.85-8.43 (m, 5H, H-5, *p*-$ClC_6\underline{H}_4$, OH), 8.00 (dd, 1H, J=4, 9, H-8), 7.65 (d, 2H, J=9, *p*-$ClC_6\underline{H}_4$). Anal. Calcd for $C_{20}H_{10}N_3O_2ClF_6$: C, 50.70; H, 2.13; N, 8.87. Found: C, 50.72; H, 2.29; N, 8.69.

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