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A FACILE AND CONVENIENT METHOD FOR THE SYNTHESIS OF 6,8-BIS(TRIFLUOROACETYL)QUINOLIN-5-AMINES

Dai Shibata,[a] Maurice Médebielle,[b] Mizuki Hatakenaka,[c] and Etsuji Okada[c,*]

[a]Graduate School of Science and Technology, Kobe University, Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan

[b]Université de Lyon, Université Claude Bernard Lyon 1 (UCBL), Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS), Laboratoire de Synthése de Biomolécules (LSB), UMR 5246 CNRS-UCBL-INSA Lyon-CPE Lyon, 43 Bd Novembre, Villeurbanne 69622, France

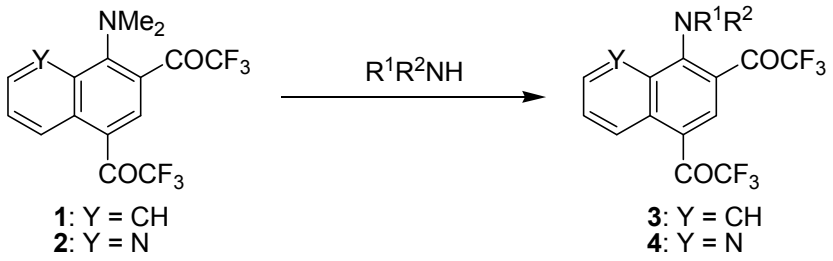
[c]Department of Chemical Science and Engineering, Graduate School of Engineering, Kobe University, Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan
E-mail: okaetsu@kobe-u.ac.jp

Abstract – New 6,8-bis(trifluoroacetyl)quinolin-5-amines (**6**) were easily prepared in moderate to high yields by the aromatic nucleophilic nitrogen-nitrogen exchange reaction of *N*,*N*-dimethyl-6,8-bis(trifluoroacetyl)-quinolin-5-amine (**5**) with various aliphatic and aromatic amines.

The quinoline skeleton has a ubiquitous presence in many natural products having significant biological activities and quinoline derivatives have wide applications in medicinal chemistry.[1] In particular, many quinoline amines, which are represented by quinolin-4-amines such as chloroquine and amodiaquine, are recognized as pharmaceutically important compounds.[2] Similarly, quinolin-5-amines have also been found to have interesting biological activities such as 5-HT_1 receptor antagonist[3a-c] and NHE-1 inhibitor.[3d] Furthermore, quinolin-5-amines could be converted to many quinoline-fused polycyclic heterocyclic compounds, for example pyrrolo[2,3-*f*]qunolines[4a] and 1,7-phenanthrolines,[5a,5b] which also indicate a variety of biological properties,[4,5] by using various ring formation reactions. Besides, significant attention in recent years 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 valuable materials showing interesting biological activities and for their potential use in medicinal and agricultural scientific fields.[6] Therefore, the development of new efficient synthetic methods for fluorine-containing quinolin-5-amine derivatives is very meaningful due to not only their own bioactivities, but also the availability as building blocks of fluorine-containing heterocycles.

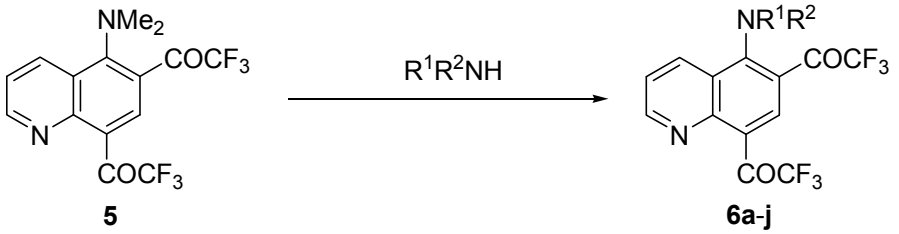
Previously, we have reported that *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)naphthalen-1-amine (**1**) and *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)quinolin-8-amine (**2**) undergo novel aromatic nucleophilic substitutions with amines under mild conditions to give the corresponding *N*-substituted 2,4-bis(trifluoroacetyl)naphthalen-1-amines (**3**)[7] and 5,7-bis(trifluoroacetyl)quinolin-8-amines (**4**),[8] respectively (Scheme 1). Moreover, we succeeded in extending this type of aromatic nucleophilic substitution to the simple syntheses of various trifluoromethyl-containing heterocycles with naphthalene[9] and quinoline[10] skeletons.



Scheme 1

Herein, we now wish to report the facile and convenient synthesis of new 6,8-bis(trifluoroacetyl)quinolin-5-amines (**6**), which are greatly expected to be utilized as novel bioactive compounds and novel building blocks for the construction of fluorine-containing heterocycles having quinoline skeleton, by the S_NAr reaction of *N*,*N*-dimethyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (**5**)[11] with various alkyl- and arylamines.

The requisite starting material (**5**) was easily prepared in moderate yield in three steps by reduction,[12] *N*,*N*-dimethylation,[13] and bis(trifluoroacetylation) of commercially available 5-nitroquinoline.[11] The aromatic nucleophilic substitution of **5** with various amines was examined, as shown in Scheme 1 and summarized in Table 1. The reaction of **5** with aqueous ammonia proceeded at 80 °C in acetonitrile to give 6,8-bis(trifluoroacetyl)quinolin-5-amine (**6a**) in 82% yield (entry 1). Primary aliphatic amines such as methyl-, isopropyl-, *tert*-butyl-, benzyl-, and propargylamines also reacted cleanly to provide the desired amine exchange products (**6b**-**f**) in 56-91% yields (entries 2-6). In the case of propargylamine,[11]



Scheme 2

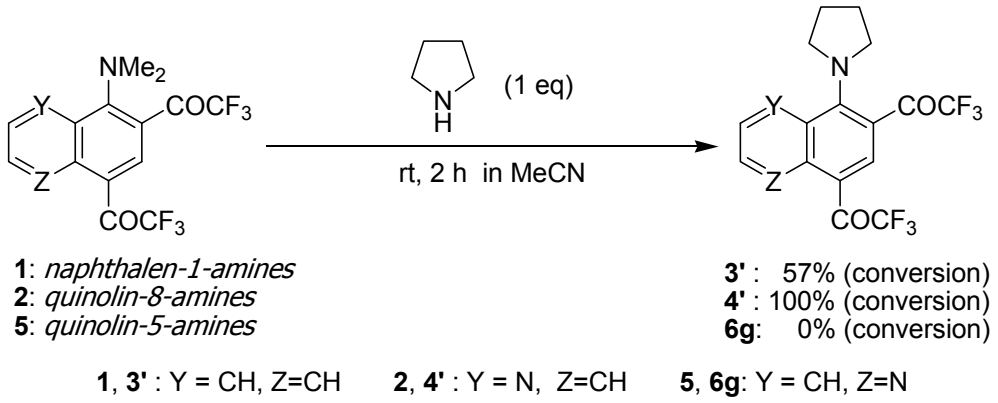
Table 1. Synthesis of 6,8-bis(trifluoroacetyl)quinolin-5-amines **6** by S_NAr reaction of **5** with amines

Entry	R^1	R^2	R^1R^2NH (eq)	Temp. (°C)	Time (h)	Solvent	Product	Yield[a] (%)
1	H	H[b]	10	80[c]	4	MeCN	**6a**	82
2	Me	H[d]	10	reflux	8	MeCN	**6b**	91
3	*i*-Pr	H	3	50	2	MeCN	**6c**	77
4	*t*-Bu	H	10	reflux	24	MeCN	**6d**	76
5	$PhCH_2$	H	1	reflux	1	MeCN	**6e**	84
6	$CH\equiv CCH_2$	H	3	reflux	2	MeCN	**6f**	56 [e]
7	$-(CH_2)_4-$		3	reflux	18	MeCN	**6g**	62
8	4-$MeOC_6H_4$	H	3	reflux	8	MeCN	**6h**	69
9	Ph	H	3	reflux	8	PrCN	**6i**	67
10	4-ClC_6H_4	H	3	reflux	18	PrCN	**6j**	69

a) Isolated yields.
b) Aqueous solution (28%) of ammonia was used.
c) In a sealed tube.
d) Aqueous solution (40%) of methylamine was used.
e) 1-(3-Dimethylaminomethyl-4-trifluoromethyl-1,7-phenanthrolin-6-yl)-2,2,2-trifluoroethane-1,1-diol was also obtained as a by-product in 34% yield. See ref. 11.

the pyridine-ring formation reaction of the desired product (**6f**)[11,14] with dimethylamine, which was generated by the elimination of the dimethylamino group from **5**, also occurred *in situ* to afford 1-(3-dimethylaminomethyl-4-trifluoromethyl-1,7-phenanthrolin-6-yl)-2,2,2-trifluoroethane-1,1-diol as a by-product in 34% yield. In addition, the reaction of **5** with secondary amine, pyrrolidine, also took place to give the desired pyrrolidino derivative (**6g**) in 62% yield (entry 7). Less nucleophilic aromatic amines such as *p*-anisidine, aniline, and *p*-chloroaniline were also found to be usable for this type of exchange reaction and thus the introduction of arylamino groups into the 5-position of quinoline system was readily achieved (entries 8-10).

It was also found that there is a great difference in reactivity among three substrates, naphthalen-1-amines (**1**), quinolin-8-amines (**2**), and quinolin-5-amines (**5**). For example, the results of the amine exchange reaction of **1**, **2**, and **5** with pyrrolidine were shown in Scheme 3. The reactivities decreased in the following order, quinolin-8-amines (**2**) > naphthalen-1-amines (**1**) > quinolin-5-amines (**5**). The difference between quinolin-8-amines (**2**) and naphthalen-1-amines (**1**) is expectedly and depends on the



Scheme 3

difference in electron-withdrawing abilities between the pyridine and benzene rings being fused into the benzene ring where the amine exchange reaction takes place. However, in striking contrast to the expected increase in reactivity of quinolin-8-amines (**2**), the reactivity of quinolin-5-amines (**5**) was dramatically decreased and became lowest among three substrates. It is noteworthy that there is an exceedingly great difference between quinolin-8-amine system (**2**) and quinolin-5-amine one (**5**), although the reason is not known at present.

In summary, we have demonstrated a facile and convenient approach for the syntheses of various 6,8-bis(trifluoroacetyl)quinolin-5-amines (**6**) which are not easily accessible by other methods, by the amine exchange reaction of *N*,*N*-dimethyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (**5**) as a key step, starting from commercially available 5-nitroquinoline. Evaluation of biological activities of new fluorine-containing compounds (**6**) and the investigations of their synthetic applications are now under way.

EXPERIMENTAL

Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured on a Bruker Avance 500 spectrometer (^{1}H at 500 MHz, ^{13}C at 126 MHz); TMS was used as an internal standard. IR spectra were recorded on a PerkinElmer Spectrum ONE spectrophotometer. Microanalyses were obtained with a Yanaco CHN-Coder MT-5 analyzer.

Aromatic Nucleophilic Substitution of *N*,*N*-Dimethyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (5) with Amines; General Procedure

The appropriate amine (0.3-3 mmol) was added to a solution of **5** (109 mg, 0.3 mmol) in MeCN or PrCN (2.4 mL), and the mixture was stirred at 50 °C, at 80 °C or under reflux for 1-24 h. Evaporation of the solvent in vacuo gave a crude mixture, which was subjected to column chromatography (silica gel, *n*-hexane-EtOAc, 5:1 to 1:1) to give the corresponding **6a-j**, **7**.

6,8-Bis(trifluoroacetyl)quinolin-5-amine (6a): mp 220 °C (*n*-C_6H_{14}/EtOAc); IR (KBr): 3520, 3323, 1662, 1623 cm^{-1}; ^1H NMR ($CDCl_3$): δ (monohydrate form) 8.89 (d, *J* = 4.5 Hz, 1H, H-2), 8.60-8.03 (br, 2H, NH or OH), 8.56 (d, *J* = 9.0 Hz, 1H, H-4), 8.40 (s, 1H, H-7), 7.63 (br s, 2H, NH or OH), 7.54 (dd, *J* = 4.5, 9.0 Hz, 1H, H-3). Anal. Calcd for $C_{13}H_6F_6N_2O_2 \cdot H_2O$: C, 44.08; H, 2.28; N, 7.91. Found: C, 43.90; H, 2.48; N, 7.68.

***N*-Methyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (6b):** mp 138-139 °C (*n*-C_6H_{14}/EtOAc); IR (KBr): 3311, 1643, 1616 cm^{-1}; ^1H NMR ($CDCl_3$): δ (monohydrate form) 10.65 (br s, 1H, NH), 8.83-8.81 (m, 2H, H-2, H-4), 8.42 (s, 1H, H-7), 7.44 (dd, *J* = 4.5, 9.0 Hz, 1H, H-3), 7.23 (br s, 2H, OH), 3.57 (d, *J* = 5.5 Hz, 3H, CH_3). Anal. Calcd for $C_{14}H_8F_6N_2O_2 \cdot H_2O$: C, 45.66; H, 2.74; N, 7.61. Found: C, 45.47; H, 2.87; N, 7.68.

***N*-Isopropyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (6c):** mp 106-107 °C (*n*-C_6H_{14}/EtOAc); IR (KBr): 3336, 1644, 1609 cm^{-1}; ^1H NMR (CD_3CN): δ (monohydrate form) 10.15-9.63 (br, 1H, NH), 8.72-8.47 (m, 2H, H-2, H-4), 8.23-7.85 (m, 3H, H-7,OH), 7.37 (dd, *J* = 5.0, 9.0 Hz, 1H, H-3), 4.70-3.92 (m, 1H, CH), 1.38 (d, *J* = 6.0 Hz, 6H, CH_3). Anal. Calcd for $C_{16}H_{12}F_6N_2O_2 \cdot H_2O$: C, 48.49; H, 3.56; N, 7.07. Found: C, 48.45; H, 3.78; N, 6.89.

***N-tert*-Butyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (6d):** mp 110-111 °C (*n*-C_6H_{14}/EtOAc); IR (KBr): 3338, 1646, 1620 cm^{-1}; ^1H NMR (CD_3CN): δ 9.14-8.83 (m, 2H, H-2, H-4), 8.53 (br s, 2H, H-7, NH), 7.72 (dd, *J* = 4.0, 9.0 Hz, 1H, H-3), 1.36 (s, 9H, CH_3). Anal. Calcd for $C_{17}H_{14}F_6N_2O_2 \cdot H_2O$: C, 49.76; H, 3.93; N, 6.83. Found: C, 49.98; H, 4.05; N, 6.73.

***N*-Benzyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (6e):** mp 207-209 °C (dec.) (*n*-C_6H_{14}/EtOAc); IR (KBr): 3336, 1633, 1616 cm^{-1}; ^1H NMR (CD_3CN): δ (monohydrate form) 10.42-10.02 (br, 1H, NH), 8.72-8.35 (m, 2H, H-2, H-4), 8.18-7.47 (m, 3H, H-7, OH), 7.30-7.00 (m, 6H, H-3, Ph), 4.83 (d, *J* = 6.0 Hz, 2H, CH_2). Anal. Calcd for $C_{20}H_{12}F_6N_2O_2 \cdot H_2O$: C, 54.06; H, 3.18; N, 6.30. Found: C, 54.07; H, 3.38; N, 6.25.

5-(Pyrrolidin-1-yl)-6,8-bis(trifluoroacetyl)quinoline (6g): mp 137-138 °C (*n*-C_6H_{14}/EtOAc); IR (KBr): 3389, 3236, 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.97 (d, *J* = 4.0 Hz, 1H, H-2), 8.61 (s, 1H, H-7), 8.35 (d, *J* = 8.0 Hz, 1H, H-4), 7.37 (dd, *J* = 4.0, 8.0 Hz, 1H, H-3), 3.67 (br s, 4H, NCH_2), 2.08 (br s, 4H, CH_2). Anal. Calcd for $C_{17}H_{12}F_6N_2O_2$: C, 52.32; H, 3.10; N, 7.18. Found: C, 52.04; H, 3.39; N, 7.17.

***N*-4-Methoxyphenyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (6h):** mp 128-133 °C (dec.) (*n*-C_6H_{14}/EtOAc); IR (KBr): 3446, 1650, 1612 cm^{-1}; ^1H NMR ($CDCl_3$): δ (monohydrate form) 11.16 (br s, 1H, NH), 8.57 (dd, *J* = 2.0, 4.0 Hz, 1H, H-2), 8.37 (br s, 1H, H-7), 8.12 (dd, *J* = 2.0, 9.0 Hz, 1H, H-4), 7.30-6.13 (br, 2H, OH), 7.12-6.68 (m, 5H, H-3, H_{arom}), 3.80 (s, 3H, OCH_3). Anal. Calcd for $C_{20}H_{12}F_6N_2O_3$: C, 54.31; H, 2.73; N, 6.33. Found: C, 54.39; H, 2.88; N, 6.10.

***N*-Phenyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (6i):** mp 115-116 °C (*n*-C_6H_{14}/EtOAc); IR (KBr): 3304, 1660, 1613 cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.18 (br s, 1H, NH), 8.79 (d, *J* = 3.0 Hz, 1H, H-2), 8.56 (br s, 1H, H-7), 8.29 (d, *J* = 9.0 Hz, 1H, H-4), 7.42-7.07 (m, 6H, H-3, H_{arom}). Anal. Calcd for $C_{19}H_{10}F_6N_2O_2 \cdot H_2O$: C, 53.03; H, 2.81; N, 6.51. Found: C, 52.98; H, 2.71; N, 6.71.

***N*-4-Chlorophenyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (6j):** mp 156-157 °C (*n*-C_6H_{14}/EtOAc); IR (KBr): 3336, 1660, 1615 cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.00 (br s, 1H, NH), 8.83 (d, *J* = 4.5 Hz, 1H, H-2), 8.57 (br s, 1H, H-7), 8.28 (d, *J* = 8.5 Hz, 1H, H-4), 7.30 (d, *J* = 8.5 Hz, 2H, H_{arom}), 7.23 (dd, *J* = 4.5, 8.5 Hz, 1H, H-3), 7.00 (d, *J* = 8.5 Hz, 2H, H_{arom}). Anal. Calcd for $C_{19}H_9ClF_6N_2O_2 \cdot H_2O$: C, 49.10; H, 2.39; N, 6.03. Found: C, 49.13; H, 2.51; N, 5.88.

Comparison of Reactivity among Naphthalen-1-amines (1), Quinolin-8-amines (2), and Quinolin-5-amines (5) in the N-N Exchange Reaction with Pyrrolidine; General Procedure

Pyrrolidine (71.1 mg, 1 mmol) was added to a solution of the appropriate substrate (1 mmol) in MeCN (8.0 mL), and the mixture was stirred at room temperature (23 °C) for 2 h. The prompt evaporation of the solvent and the remained pyrrolidine under the reduced pressure at room temperature gave a crude mixture. The conversion was determined by ^1H NMR measurement of the crude reaction mixtures (calculated from integration ratio between methyl protons of dimethylamino group and methylene protons of pyrroridinyl group).

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