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A FACILE AND CONVENIENT SYNTHETIC METHOD FOR FLUORINE-CONTAINING 1*H*-PYRROLO[3,2-*h*]QUINOLINES

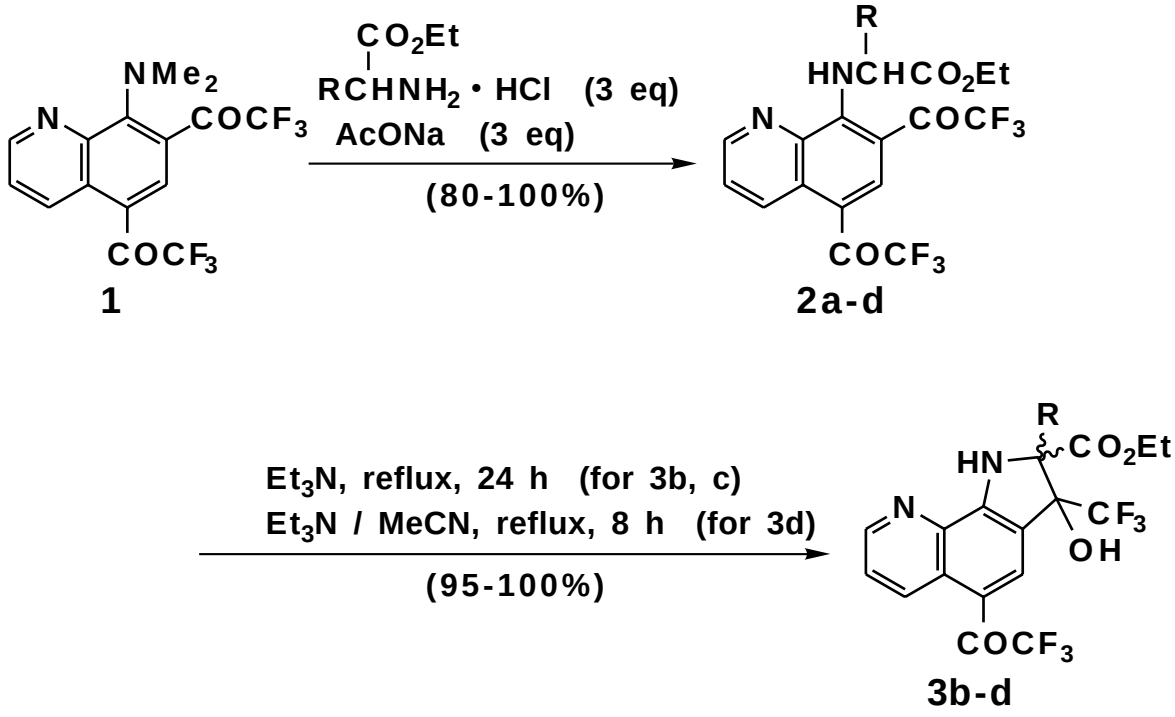
Etsuji Okada* and Norikado Tsukushi

Department of Chemical Science and Engineering, Faculty of Engineering, Kobe University, Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan

Abstract - Aromatic nucleophilic nitrogen-nitrogen exchange reaction of *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine (**1**) with some amino acid derivatives gave the corresponding *N*-[5,7-bis(trifluoroacetyl)-8-quinolyl]amino acid derivatives (**2**) in excellent yields. Base-catalyzed cyclization of **2** afforded fluorine-containing 1*H*-pyrrolo[3,2-*h*]quinolines (**3**, **4**) in high yields.

In recent years much 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] We have recently reported that *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine (**1**) undergoes a novel aromatic nucleophilic substitution with amines to give the corresponding 5,7-bis(trifluoroacetyl)-8-quinolylamines and its application to the simple synthesis of 2-ethoxycarbonyl-5-trifluoroacetyl-3-trifluoromethyl-1*H*-pyrrolo[3,2-*h*]quinoline (**4**).[2] Pyrroloquinoline and the related derivatives are very important heterocyclic systems, constituting the structure of many naturally occurring products and having interesting biological activities.[3] In particular, 1*H*-pyrrolo[3,2-*h*]quinoline derivatives not only show important pharmacological properties such as tuberculostatic[4] and antiproliferative[5] activities but also can be considered as electronic structural and behavioral intermediates between 7-azaindole and 4-hydroxy-5-azaphenanthrene.[6] In this paper, we wish to report a full account of

extensive works on the pyrroloquinoline ring forming reaction of **1** with various amino acid derivatives. First, we examined aromatic nucleophilic nitrogen-nitrogen exchange reactions of **1** with amino acid derivatives, as shown in Scheme 1 and summarized in Table 1. Reaction of **1** with glycine ethyl ester



2, 3	a	b	c	d
R	H	Me	CH_2CH_2SMe	Ph

Scheme 1

hydrochloride proceeded easily at room temperature for 6 h in acetonitrile/water in the presence of sodium acetate to afford *N*-[5,7-bis(trifluoroacetyl)-8-quinolyl]glycine ethyl ester (**2a**) in quantitative yield. In the cases of alanine and methionine ethyl esters, refluxing in the same solvent was required for completing the reactions and the corresponding amino acid derivatives (**2b**, **c**) were obtained in excellent yields. In contrast to the results mentioned above, reaction of **1** with phenylglycine ethyl ester hydrochloride and sodium acetate in refluxing acetonitrile/water for 6 h provided not only the desired trifluoroacetylated *N*-(8-quinolyl)phenylglycine ethyl ester (**2d**) in 57% yield but also 2,3-dihydro-1*H*-pyrrolo[3,2-*h*]quinoline (**3d**) in 38% yield. Both higher temperature (in refluxing butyronitrile/water) and shorter reaction time (for 0.5

h) were necessary in order to obtain the desired product (**2d**) in more excellent yield (80%) by suppressing subsequent cyclization to **3d** (20%).

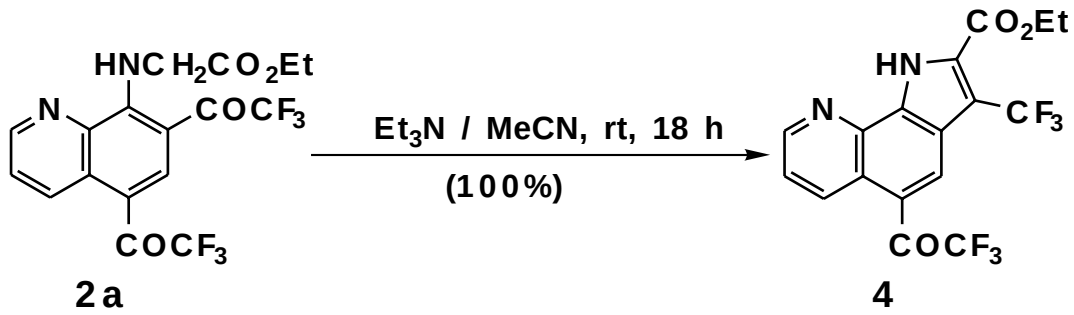
Table 1. Syntheses of *N*-[5,7-Bis(trifluoroacetyl)-8-quinolyl]amino Acid Derivatives (**2a-d**) and 1*H*-Pyrrolo[3,2-*h*]quinolines (**3b-d,4**)

Entry	Substrate	Solvent	Temp.	Time (h)	Product[a)]	Yield (%)[b)]
1	**1**	MeCN / H_2O (9 : 1)	rt	6	**2a**	100
2	**1**	MeCN / H_2O (9 : 1)	reflux	6	**2b**	94
3	**1**	MeCN / H_2O (9 : 1)	reflux	6	**2c**	94
4	**1**	PrCN / H_2O (9 : 1)	reflux	0.5	**2d**	80[c)]
5	**2a**	MeCN	rt	18	**4**	100
6	**2b**	Et_3N	reflux	24	**3b**	98
7	**2c**	Et_3N	reflux	24	**3c**	95
8	**2d**	MeCN	reflux	8	**3d**	100
9	**1**	MeCN	rt	18	**4**	94
10	**1**	Et_3N	reflux	24	**3b**	93
11	**1**	Et_3N	reflux	24	**3c**	98
12	**1**	MeCN	reflux	8	**3d**	100

a) Products (**3b-d**)were mixtures of the two stereoisomers. b) Isolated yields. c) With 20% yield of **3d**.

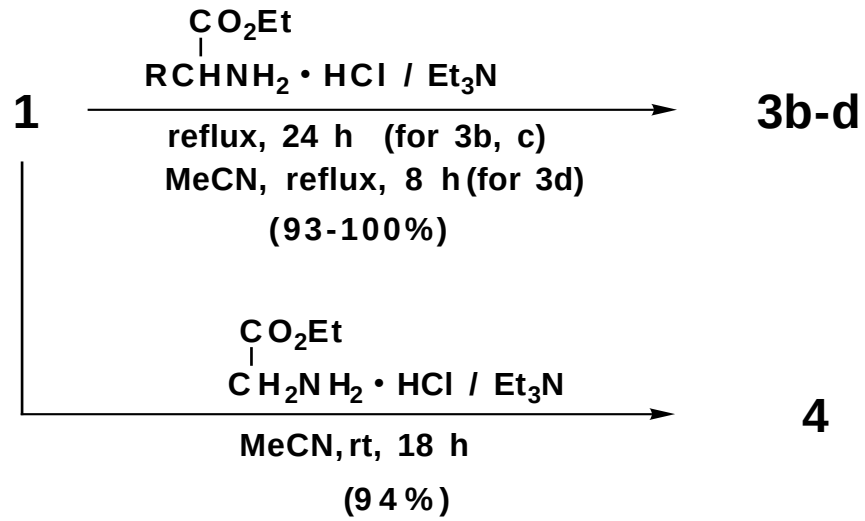
Next, we attempted to run the cyclization of **2a-d** into the desired 1*H*-pyrrolo[3,2-*h*]quinolines. Base-catalyzed cyclization of amino acid derivatives (**2b-d**) with the use of triethylamine instead of sodium acetate proceeded at reflux temperature for 8 - 24 h to provide the desired 2,3-dihydro-1*H*-pyrrolo[3,2-*h*]-quinolines (**3b-d**) in over 95% yields. Products (**3b-d**) were found to consist of two possible stereoisomers.[7] However, as depicted in Scheme 2, in the case of **2a** cyclization and subsequent dehydration was smoothly took place even at room temperature for 18 h in the presence of triethylamine to give 1*H*-pyrrolo[3,2-*h*]quinoline (**4**) quantitatively without being accompanied by the corresponding 2,3-

dihydro-1*H*-pyrrolo[3,2-*h*]quinoline (**3a**).



Scheme 2

Further, we tried to carry out the present pyrroloquinoline ring forming reaction in a one-pot manner starting from **1**, as shown in Scheme 3. *N*,*N*-Dimethyl-8-quinolylamine derivative (**1**) reacted with alanine, methionine, and phenylglycine ethyl ester hydrochlorides in refluxing triethylamine or in refluxing acetonitrile in the presence of triethylamine to afford 2,3-dihydro-1*H*-pyrrolo[3,2-*h*]quinolines (**3b-d**) in high yields. Similarly, 1*H*-pyrrolo[3,2-*h*]quinoline (**4**) could be also synthesized easily in 94% yield. In



Scheme 3

the use of a large excess of triethylamine, the cyclization of intermediary *N*-(8-quinolyl)amino acid derivatives (**2**) to 1*H*-pyrrolo[3,2-*h*]quinolines (**3**, **4**) is promoted by triethylamine as a base catalyst. However, in the use of triethylamine in amounts equimolar with amino acid hydrochlorides, resulting free amino acid ethyl esters would also act as a base and prompt the cyclization of 2 to 3 and 4. In contrast to

this, in the use of sodium acetate instead of triethylamine, acetic acid would be generated *in situ*, so that the reaction system would be made acidic weakly to suppress subsequent base-catalyzed cyclization of **2** to **3** and **4**.

Thus, the present method provides a facile and convenient access to 1*H*-pyrrolo[3,2-*h*]quinolines 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.

Synthesis of *N*-[5,7-Bis(trifluoroacetyl)-8-quinolyl]amino Acid Derivatives (2a-d); General Procedure: A mixture of **1**[2] (364 mg, 1 mmol), the appropriate amino acid derivatives (3 mmol), and sodium acetate (246 mg, 3 mmol) was suspended in MeCN (6.3 mL)/H_2O (0.7 mL) and this suspension was stirred at rt or under reflux for 0.5 - 6 h. The solvent was removed under reduced pressure, and EtOAc (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 and the crude product was chromatographed using hexane/ EtOAc (7:1) for **2b-d** as eluent. In the case of **2a**, the practically pure product was obtained without purification by chromatography. In the case of **2d**, PrCN/H_2O was used as a solvent.

2a: mp 154-155 ˚C (Spectroscopic and analytical data are described in ref. 2.)

2b: mp 67-68 ˚C (hexane); IR (KBr) 3370-2270, 1735, 1683, 1647 cm^{-1}; ^{1}H-NMR 11.54-11.05 (br, 1H, NH), 9.44 (dd, 1H, J=2, 9, H-4), 8.80-8.64 (m, 2H, H-2, H-6), 7.61 (dd, 1H, J=4, 9, H-3), 6.05-5.57 (m, 1H, NCH), 4.23 (q, 2H, J=7, C$\underline{H}_2$CH$_3$), 1.72 (d, 3H, J=7, CH$_3$), 1.26 (t, 3H, J=7, CH$_2$C$\underline{H}_3$).

Anal. Calcd for $C_{18}H_{14}N_2O_4F_6$: C, 49.55; H, 3.23; N, 6.42. Found: C, 49.60; H, 3.15; N, 6.47.

2c: mp 84-85 ˚C (hexane); IR (KBr) 3290-2260, 1730, 1697, 1651 cm^{-1}; ^{1}H-NMR 11.66-11.16 (br, 1H, NH), 9.41 (dd, 1H, J=2, 9, H-4), 8.77-8.59 (m, 2H, H-2, H-6), 7.59 (dd, 1H, J=4, 9, H-3), 6.17-5.71 (m, 1H, NCH), 4.20 (q, 2H, J=7, $C\underline{H}_2CH_3$), 2.90-2.13 (m, 4H, CH_2), 2.13 (s, 3H, SCH_3), 1.25 (t, 3H, J=7, $CH_2C\underline{H}_3$). Anal. Calcd for $C_{20}H_{18}N_2O_4F_6S$: C, 48.39; H, 3.65; N, 5.64. Found: C, 48.28; H, 3.57; N, 5.62.

2d: mp 140-141 ˚C (hexane); IR (KBr) 3280-2270, 1730, 1693, 1642 cm^{-1}; ^{1}H-NMR 12.00-11.31 (br, 1H, NH), 9.42 (dd, 1H, J=2, 9, H-4), 8.81-8.58 (m, 2H, H-2, H-6), 7.70-7.22 (m, 6H, H-3, C_6H_5), 7.17-6.53 (br, 1H, NCH), 4.37-4.01 (m, 2H, $C\underline{H}_2CH_3$), 1.19 (t, 3H, J=7, $CH_2C\underline{H}_3$). Anal. Calcd for $C_{23}H_{16}N_2O_4F_6$: C, 55.43; H, 3.24; N, 5.62. Found: C, 55.44; H, 3.23; N, 5.57.

Synthesis of 2,3-Dihydro-1*H*-pyrrolo[3,2-*h*]quinolines (3b-d) and 1*H*-Pyrrolo[3,2-*h*]-quinoline (4); General Procedure:

***In Acetonitrile* :** To a solution of **2a**, **d** (1 mmol) in MeCN (8 mL) was added triethylamine (101 mg, 1 mmol) and the mixture was stirred at rt or under reflux for 8 - 18 h. The solvent was removed under reduced pressure, and EtOAc (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 and the crude product was chromatographed using hexane/EtOAc (3:1) for **3d** as eluent. In the case of **4**, the practically pure product was obtained without purification by chromatography.

***In Triethylamine* :** A solution of **2b**, **c** (1 mmol) in triethylamine (8 mL) was heated at reflux temperature for 24 h. The solvent was removed under reduced pressure, and EtOAc (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 and the crude product was chromatographed using hexane/EtOAc (3:1) for **3b** and hexane/ EtOAc (1:1) for **3c** as eluent.

3b (mixture of stereoisomers)**:** mp 171-173 ˚C (hexane/EtOAc); IR (KBr) 3300, 1721, 1679 cm^{-1}; ^{1}H-NMR ($CD_3CN/CDCl_3$) 9.57-9.30 (m, 1H, H-6), 8.79-8.53 (m, 1H, H-8), 8.18 (br s, 1H, H-4), 7.66-7.33 (m, 2H, H-7, NH or OH), 5.87-5.21 (br, 1H, NH or OH), 4.42-4.07 (m, 2H, $C\underline{H}_2CH_3$), 1.79 (br s,

3H, CH_3), 1.39-1.11 (m, 3H, $CH_2C\underline{H}_3$). Anal. Calcd for $C_{18}H_{14}N_2O_4F_6$: C, 49.55; H, 3.23; N, 6.42. Found: C, 49.55; H, 3.23; N, 6.42.

3c (mixture of stereoisomers)**:** mp 112-135 ˚C (hexane/EtOAc); IR (KBr) 3240, 1725, 1680 cm^{-1}; ^{1}H-NMR 9.66-9.43 (m, 1H, H-6), 8.88-8.66 (m, 1H, H-8), 8.30 (br s, 1H, H-4), 7.79-7.42 (m, 2H, H-7, NH or OH), 5.98-5.21 (br, 1H, NH or OH), 4.62-4.17 (m, 2H, $C\underline{H}_2CH_3$), 2.86-2.12 (m, 7H, $CH_2CH_2SCH_3$), 1.52-1.21 (m, 3H, $CH_2C\underline{H}_3$). Anal. Calcd for $C_{20}H_{18}N_2O_4F_6S$: C, 48.39; H, 3.65; N, 5.64. Found: C, 48.21; H, 3.63; N, 5.64.

3d (mixture of stereoisomers)**:** mp 199-209 ˚C (hexane/EtOAc); IR (KBr) 3365, 1746, 1706, 1683 cm^{-1}; ^{1}H-NMR ($CD_3CN/CDCl_3$) 9.62-9.44 (m, 1H, H-6), 8.86-8.73 (m, 1H, H-8), 8.39-8.16 (m, 1H, H-4), 8.00-7.18 (m, 7H, H-7, C_6H_5, NH or OH), 6.69-6.16 (br, 1H, NH or OH), 4.45-4.00 (m, 2H, $C\underline{H}_2CH_3$), 1.35-0.97 (m, 3H, $CH_2C\underline{H}_3$). Anal. Calcd for $C_{23}H_{16}N_2O_4F_6$: C, 55.43; H, 3.24; N, 5.62. Found: C, 55.16; H, 3.51; N, 5.58.

4: mp 205-206 ˚C (Spectroscopic and analytical data are described in ref. 2.)

One-Pot Synthesis of 2,3-Dihydro-1*H*-pyrrolo[3,2-*h*]quinolines (3b-d) and 1*H*-Pyrrolo-[3,2-*h*]quinoline (4) Starting from 1 and Amino Acid Derivatives; General Procedure:

***In Acetonitrile* :** To a suspension of the appropriate amino acid derivatives (3 mmol) and triethylamine (304 mg, 3 mmol) in MeCN (7 mL) was added **1** (364 mg, 1 mmol) and the mixture was stirred at rt or under reflux for 8 - 18 h. The solvent was removed under reduced pressure, and EtOAc (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 and the crude product was chromatographed to give **3d**. In the case of **4**, the practically pure product was obtained without purification by chromatography.

***In Triethylamine* :** To a suspension of the appropriate amino acid derivatives (2 mmol) in triethylamine (4 mL) was added **1** (364 mg, 1 mmol) and the mixture was stirred at reflux temperature for 24 h. The solvent was removed under reduced pressure, and EtOAc (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 and the crude product was chromatographed to give **3b**, **c**.

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7. Proportions of the two stereoisomers could not be estimated exactly; furthermore, extensive overlap of the signals did not allow individual assignments. Since all attempts to separate two isomers by TLC and recrystallization were unsuccessful, the stereochemistry of the isomers has not been determined to date.