A SIMPLE AND EFFICIENT SYNTHETIC METHOD FOR FLUORINE-CONTAINING BENZO[*b*][1,10]PHENANTHROLINES

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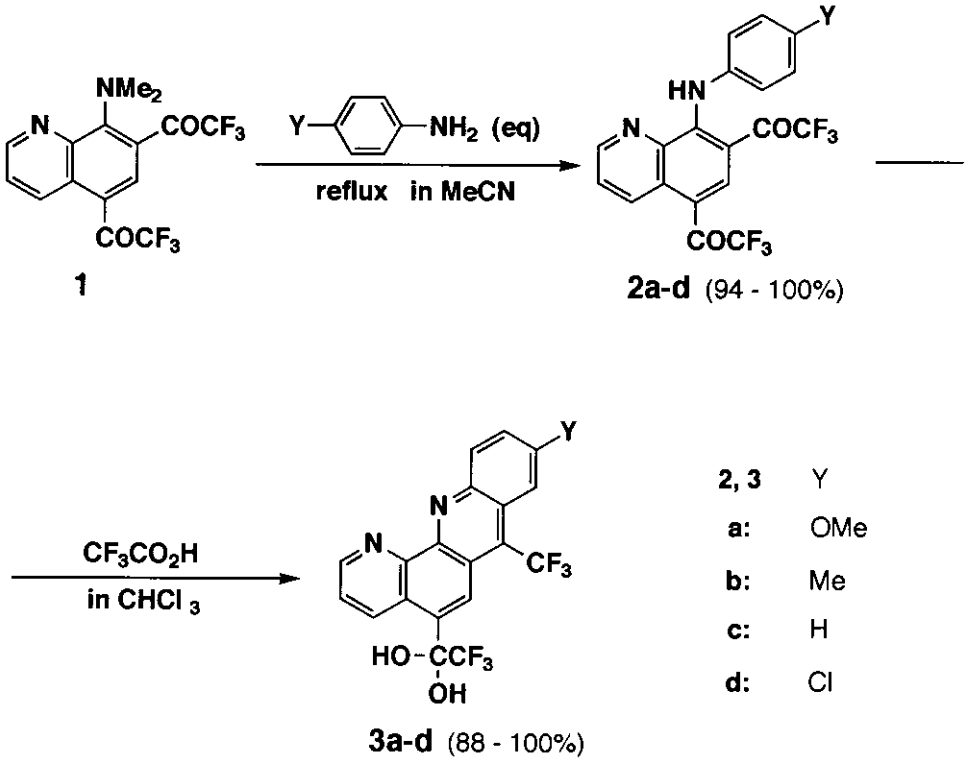
Abstract - Acid-catalyzed cyclization of *N*-aryl-5,7-bis(trifluoroacetyl)-8-quinolylamines (**2**), prepared by aromatic nucleophilic nitrogen-nitrogen exchange reaction of *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine (**1**) with *p*-substituted anilines, afforded fluorine-containing benzo[*b*][1,10]phenanthrolines (**3**) in excellent yields.

Benzo[*b*][1,10]phenanthroline and the related derivatives are important heterocyclic systems because of not only showing interesting pharmacological properties as antileukemic,[1] antithrombotic,[2] and antitumor[3] activities but also being applicable to important chelating ligands forming stable complexes with urea,[4] guanine nucleosides,[5] creatinines,[6] and transition metals.[7] Besides, considerable attention in recent years has been paid to 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.[8] So far, we have found that *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine[9] and *N*,*N*-dimethyl-2-trifluoroacetyl-4-halo-1-naphthylamines[10] react easily with various amines, thiols, and alcohols under mild conditions to afford the corresponding N-N, N-S, and N-O exchanged products in excellent yields,

respectively. Furthermore, we carried out applying this type of aromatic nucleophilic substitution and related reactions to the simple syntheses of naphthalene-fused heterocycles bearing trifluoromethyl groups.[11] On the other hand, 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.[12] Therefore, we have recently reported that *N*,*N*-dimethyl-5,7-bis(trifluoro-acetyl)-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 synthesis of fluorine-containing 1*H*-pyrrolo[3,2-*h*]quinolines.[13] In connection with these works, we now wish to report herein the facile synthesis of fluorine-containing benzo[*b*][1,10]phenanthrolines (**3**) starting from trifluoroacetylated *N*,*N*-dimethyl-8-quinolylamine (**1**) and *p*-substituted anilines.



Scheme 1

N-Aryl-5,7-bis(trifluoroacetyl)-8-quinolylamines (**2a-d**) were obtained in over 94% yields by aromatic nucleophilic dimethylamino-arylamino exchange reaction of **1** with *p*-substituted anilines in refluxing acetonitrile (Scheme 1).

Acid-catalyzed cyclization of **2a** with trifluoroacetic acid proceeded easily even at room temperature for 24 h in chloroform to afford the desired 9-methoxybenzo[*b*][1,10]phenanthroline (**3a**) in almost quantitative yield. Similarly, 9-methyl and 9-unsubstituted derivatives (**3b**, **c**) were synthesized in high yields. Compared with **2a-c** the cyclization of *p*-chloro derivative (**2d**) was difficult to proceed. 9-Chloro derivative of benzo[*b*][1,10]phenanthroline (**3d**), however, was cleanly prepared in 90% yield by merely elevating reaction temperature (50 °C) and using large excess of trifluoroacetic acid (10 equiv.).

5-Trifluoroacetyl group of benzo[*b*][1,10]phenanthrolines (**3**) was found to exist as hydrated form and this phenomenon was not observed in benz[*c*]acridine system.[11b]

Thus, the present method provides a simple and efficient access to CF_3-containing benzo-[*b*][1,10]phenanthrolines which are not easily obtained by other methods. Further work is currently continued in our laboratory 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. ^{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. 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*-Aryl-5,7-bis(trifluoroacetyl)-8-quinolylamines (2a-d); General Procedure: To a solution of **1** (364 mg, 1 mmol) in MeCN (7 mL) was added the appropriate anilines (1 mmol) and the mixture was stirred at reflux temperature for 3 h. The solvent was removed under reduced pressure to afford the practically pure **2a-d**.

The following reaction times applied; 12 h for **2c** and 24 h for **2d**.

2a: yield 100%; mp 176-177 °C (hexane/EtOAc); IR (KBr) 3250, 1683 cm^{-1}; ^{1}H-NMR 10.79-10.47 (br, 1H, NH), 9.52 (dd, 1H, J=2, 9, H-4), 8.73 (dd, 1H, J=2, 4, H-2), 8.64 (br s, 1H, H-6), 7.67 (dd, 1H, J=4, 9, H-3), 7.29-6.80 (m, 4H, *p*-$MeOC_6\underline{H_4}$), 3.82 (s, 3H, OCH_3). Anal. Calcd for $C_{20}H_{12}N_2O_3F_6$: C, 54.31; H, 2.73; N, 6.33. Found: C, 54.39; H, 2.72; N, 6.35.

2b: yield 100%; mp 191-192 °C (hexane/EtOAc); IR (KBr) 3280, 1692 cm^{-1}; ^{1}H-NMR 10.77-10.18 (br, 1H, NH), 9.59 (dd, 1H, J=2, 9, H-4), 8.82 (dd, 1H, J=2, 4, H-2), 8.72 (br s, 1H, H-6), 7.75 (dd, 1H, J=4, 9, H-3), 7.38-7.00 (m, 4H, *p*-$MeC_6\underline{H_4}$), 2.40 (s, 3H, CH_3). Anal. Calcd for $C_{20}H_{12}N_2O_2F_6$: C, 56.35; H, 2.84; N, 6.57. Found: C, 56.25; H, 2.89; N, 6.66.

2c: yield 100%; mp 192-193 °C (hexane/EtOAc); IR (KBr) 3270, 1683 cm^{-1}; ^{1}H-NMR 10.90-10.44 (br, 1H, NH), 9.48 (dd, 1H, J=2, 9, H-4), 8.74 (dd, 1H, J=2, 4, H-2), 8.61 (br s, 1H, H-6), 7.70 (dd, 1H, J=4, 9, H-3), 7.51-7.03 (m, 5H, C_6H_5). Anal. Calcd for $C_{19}H_{10}N_2O_2F_6$: C, 55.35; H, 2.44; N, 6.80. Found: C, 55.32; H, 2.44; N, 7.08.

2d: yield 94%; mp 184-185 °C (hexane/EtOAc); IR (KBr) 3235, 1687 cm^{-1}; ^{1}H-NMR 10.95 (br s, 1H, NH), 9.47 (dd, 1H, J=2, 9, H-4), 8.75-8.60 (m, 2H, H-2, -6), 7.67 (dd, 1H, J=4, 9, H-3), 7.44-6.96 (m, 4H, *p*-$ClC_6\underline{H_4}$). Anal. Calcd for $C_{19}H_9N_2O_2ClF_6$: C, 51.08; H, 2.03; N, 6.27. Found: C, 51.05; H, 2.19; N, 6.51.

Synthesis of Benzo[*b*][1,10]phenanthrolines (3a-d); General Procedure: To a solution of **2a-d** (1 mmol) in $CHCl_3$ (3 mL) was added CF_3CO_2H (570 mg, 5 mmol). The mixture was stirred at rt for 6 h, the solvent was removed under reduced pressure, and CH_2Cl_2 (200 mL) was added to the residue. The solution was washed with saturated solution of Na_2CO_3 (200 mL) and dried (Na_2SO_4). The solvent was evaporated to afford the practically pure **3a-d**.

The reaction time was 24 h for **3a**. In the case of **3d**, 10 mmol (1.1 g) of TFA was used to 1 mmol of **2d** and the reaction was carried out at 50 °C for 24 h.

3a: yield 99%; mp 204 °C (decomp); IR (KBr) 3340 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3) 9.47-9.09 (m, $2H_{arom}$), 8.94 (br s, $1H_{arom}$), 8.82-8.38 (m, 3H, $2H_{arom}$, OH), 7.98-7.54 (m, 3H, $2H_{arom}$, OH), 4.02 (s, 3H,

OCH_3). Anal. Calcd for $C_{20}H_{12}N_2O_3F_6$: C, 54.31; H, 2.73; N, 6.33. Found: C, 54.18; H, 3.00; N, 6.19.

3b: yield 88%; mp 187-188 °C; IR (KBr) 3310 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3) 9.47-9.12 (m, $2H_{arom}$), 8.96 (br s, $1H_{arom}$), 8.55-8.34 (m, 4H, $2H_{arom}$, OH), 8.10-7.75 (m, $2H_{arom}$), 2.69 (s, 3H, CH_3). Anal. Calcd for $C_{20}H_{12}N_2O_2F_6$: C, 56.35; H, 2.84; N, 6.57. Found: C, 56.21; H, 2.86; N, 6.62.

3c: yield 100%; mp 193-194 °C; IR (KBr) 3325 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3) 9.54-9.20 (m, $2H_{arom}$), 9.03 (br s, $1H_{arom}$), 8.70-8.48 (m, 4H, $2H_{arom}$, OH), 8.22-7.84 (m, $3H_{arom}$). Anal. Calcd for $C_{19}H_{10}N_2O_2F_6$: C, 55.35; H, 2.44; N, 6.80. Found: C, 55.08; H, 2.66; N, 6.84.

3d: yield 90%; dec 202 °C; IR (KBr) 3290 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3) 9.41-9.08 (m, $2H_{arom}$), 8.88 (br s, $1H_{arom}$), 8.62-8.38 (m, 4H, $2H_{arom}$, OH), 8.14-7.73 (m, $2H_{arom}$). Anal. Calcd for $C_{19}H_9N_2O_2ClF_6$: C, 51.08; H, 2.03; N, 6.27. Found: C, 51.09; H, 2.30; N, 5.99.

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