A SIMPLE AND EFFICIENT SYNTHETIC METHOD FOR FLUORINE-CONTAINING BENZO[*h*]QUINOLINES

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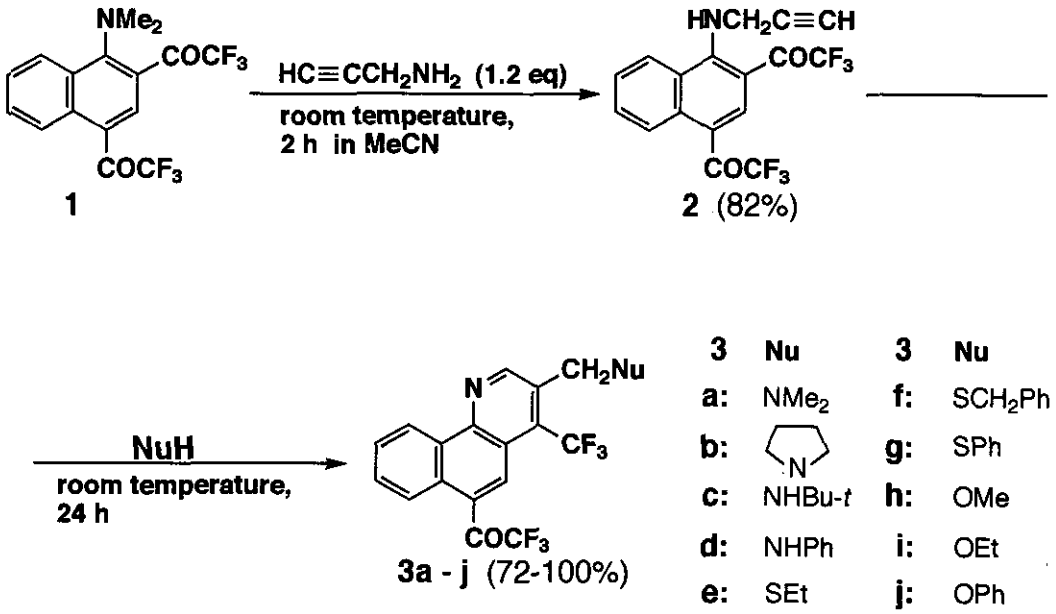
Abstract - *N*-Propargyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**2**), prepared from *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**) and propargylamine, undergoes ring forming reaction with amines, thiolates and alcoholates under mild conditions to afford the corresponding 6-trifluoroacetyl-4-trifluoromethylbenzo[*h*]quinolines (**3**) in excellent yields.

Benzoquinoline derivatives are important heterocyclic systems, constituting the structure of many naturally occurring products and having interesting pharmacological properties as antimicrobial agents and antitumor drugs.[1-5] 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 science.[6-9] Previously, we reported that *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**) undergoes a novel aromatic nucleophilic substitution with various amines, thiols, and alcohols to give the corresponding 2,4-bis(trifluoroacetyl)-1-naphthylamines, sulfides, and ethers in high yields.[10-13] Later, we succeeded in applying this type of aromatic nucleophilic substitution and the related reactions to the simple syntheses of various naphthalene-fused heterocycles bearing trifluoromethyl groups (benzindoles,[14] naphthothiophenes,[15] benzacridines,[16] benzothioxanthenes,[17] benzoxanthenes,[17] benzindazoles,[18] benzoquinazolines,[19] naphthoisoxazoles,[18] naphthoxazines,[20,21] naphthothiazines[22]). In connection with these works, we now report here that the title compounds (**3**) can be very easily synthesized by the ring forming reaction of **1** with various *N*-, *S*- and *O*- nucleophiles.

N-Propargyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**2**) was readily synthesized in 82% yield by the

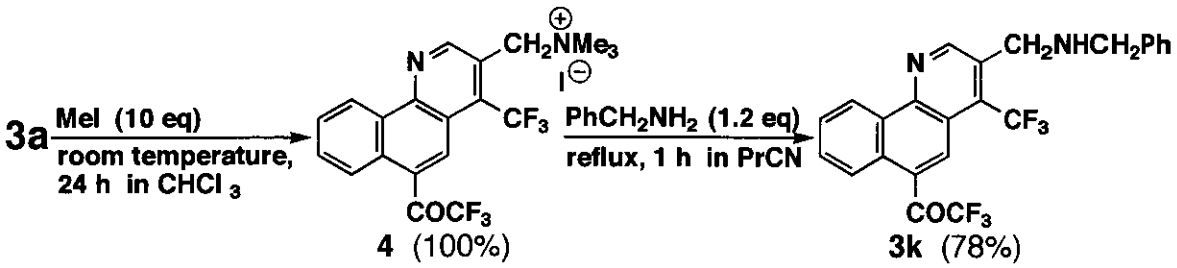
aromatic nucleophilic N-N exchange reaction of *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**)[10] with propargylamine at room temperature for 2 h (Scheme 1).[23] We first examined the synthesis of the desired fluorine-containing benzo[*h*]quinolines by the ring closure reaction of **2** with various amines. Cyclization of **2** with aqueous dimethylamine proceeded cleanly in acetonitrile at room temperature for 24 h to give 6-trifluoroacetyl-4-trifluoromethyl-3-dimethylaminomethylbenzo[*h*]quinoline (**3a**) almost quantitatively without any formation of propargylamino-dimethylamino exchanged product (**1**). 3-(1-Pyrrolidin-



Scheme 1

yl)methyl derivative (**3b**) was obtained in 77% yield through the reaction of **2** with pyrrolidine, though N-N exchanged product, *N*,*N*-tetramethylene-2,4-bis(trifluoroacetyl)-1-naphthyl-amine,[10,21] was formed in 9% yield. Bulky primary amines such as *tert*-butylamine smoothly underwent the similar cyclization with **2** to afford solely the corresponding benzo[*h*]quinoline derivative (**3c**) in 96% yield. Unfortunately, in the reaction of **2** with aqueous ammonia and less bulky primary amines such as aqueous methylamine and benzylamine, aromatic nucleophilic substitution reaction proceeded in preference to the desired ring forming one to give the corresponding N-N exchanged products in quantitative yields. However, we could find an alternative route for the synthesis of 3-alkylaminomethylbenzo[*h*]quinolines which are not obtained directly from **2** and primary amines. As depicted in Scheme 2, for example, 3-benzylaminomethyl derivative (**3k**) could be synthesized in 78% yield by the N-N exchange reaction of benzylamine with

quaternary ammonium salt (**4**), which is obtained quantitatively from 3-dimethylaminomethyl derivative (**3a**) with methyl iodide. As aromatic amines, aniline also reacted cleanly in the presence of triethylamine as a base to provide phenylaminomethyl derivative (**3d**) in 80% yield. In the absence of triethylamine, **3d** was not obtained and starting material (**2**) was recovered quantitatively.



Scheme 2

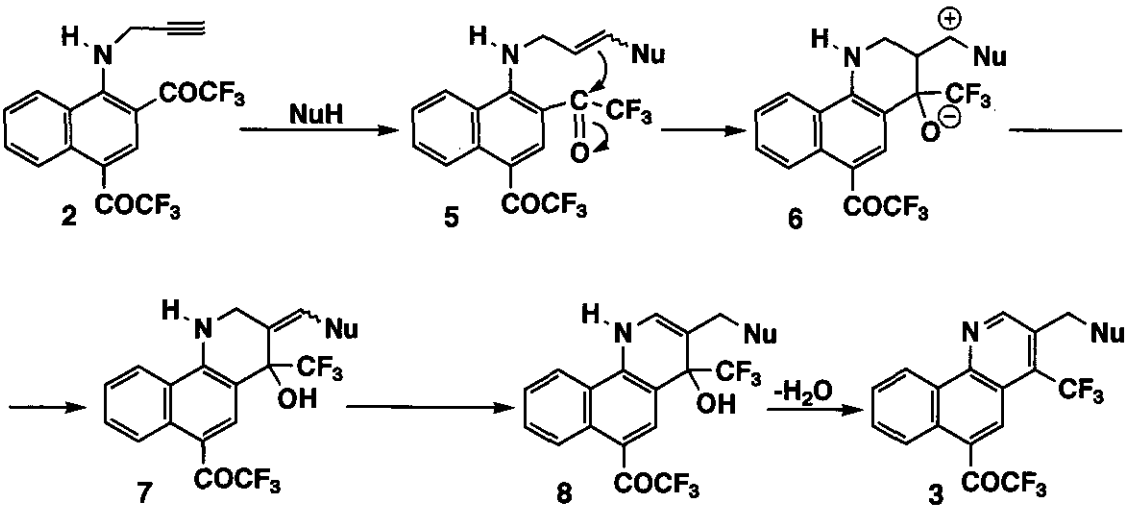
Next we attempted to carry out the present cyclization using thiols in order to obtain fluorine-containing benzo[*h*]quinolines having alkyl(or aryl)thiomethyl substituent at the 3-position. Reactions of **2** with thiols hardly took place without the aid of bases, so that the use of thiolates was required for the intended ring closure. *N*-Propargyl-1-naphthylamine derivative (**2**) reacted easily with sodium ethanethiolate, phenylmethanethiolate, and benzenethiolate at room temperature within 24 h to yield the desired benzo[*h*]quinolines (**3e-g**) in 72-100% yields.

Similarly, ring forming reaction of **2** with some alcoholates such as methanolate, ethanolate, and phenolate proceeded easily at room temperature to give the corresponding 3-alkyl(or aryl)oxymethyl-benzo[*h*]quinolines (**3h-j**) in 72-98% yields.[24]

A possible mechanism for the present benzoquinoline ring forming reaction is as shown in Scheme 3. *N*-Allyl derivative (**5**) is produced by nucleophilic attack of NuH (nucleophile) onto the terminal acetylenic carbon of *N*-propargyl group of **2**.[25] Subsequently, carbon-carbon bond formation between internal olefinic carbon of *N*-allyl group and carbonyl carbon occurs to give the cyclized product (**7**) *via* **6**. Following 1,3-H shift dehydration takes place to afford benzo[*h*]quinoline (**3**).

The structures of all new compounds (**2-4**) were determined on the basis of their ^{1}H-NMR and IR spectra, together with elemental analyses. As a representative case, benzo[*h*]quinoline (**3a**) was further confirmed by ^{13}C-NMR spectral data.

Thus, the present method provides a simple and efficient access to CF_3-containing benzo[*h*]quinolines which are not easily obtained by other methods. Further investigations on the present heterocyclic ring



Scheme 3

forming reaction of **2** with nucleophiles, for instance, C-nucleophiles such as active methylene compounds, are currently under way and will be published in our forthcoming papers. Evaluation of biological activities for **3** is also in progress.

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- and ^{13}C-NMR spectra were obtained with JEOL PMX 60SI and FX 90Q instruments 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 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*-Propargyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (2): To a solution of **1**[10] (3633 mg, 10 mmol) in MeCN (80 mL) was added propargylamine (661 mg, 12 mmol) and the solution was stirred at room temperature for 2 h. Removal of the solvent under reduced pressure gave the crude mixture which was chromatographed using hexane/benzene (7:3) for **2** (3056 mg, 8.2 mmol) and benzene/EtOAc (19:1) for by-product (**3a**) (721 mg, 1.8 mmol) as eluent.

2: yield 82%; mp 140-141 °C (hexane/$CHCl_3$); IR (KBr) 3310, 3135, 1685, 1657 cm^{-1}; ^{1}H-NMR 10.98-

10.33 (br, 1H, NH), 9.11-8.94 (m, 1H, H-5), 8.57 (br s, 1H, H-3), 8.39-8.23 (m, 1H, H-8), 7.91-7.28 (m, 2H, H-6, -7), 4.57 (dd, J=2.5, 6, 2H, CH_2), 2.55 (t, J=2.5, 1H, ≡CH). Anal. Calcd for $C_{17}H_9NO_2F_6$: C, 54.70; H, 2.43; N, 3.75. Found: C, 54.48; H, 2.54; N, 3.92.

Reaction of *N*-Propargyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (2) with Amines; General Procedure: To a solution of **2** (373 mg, 1 mmol) in MeCN (8 mL) was added the appropriate amine (1 mmol) and the solution was stirred at room temperature for 24 h. The solvent was evaporated *in vacuo* and the crude product was chromatographed using benzene/EtOAc (9:1) for **3b**, benzene/EtOAc (19:1) for **3a**, benzene for **3c**, and hexane/benzene (3:7) for **3d** as eluent.

In the synthesis of **3c**, 3 mmol of amine were used to 1 mmol of **2**. In the synthesis of **3d**, 2 mmol of amine and 2 mmol of Et_3N were used to 1 mmol of **2**.

In the case of **3b**, *N*,*N*-tetramethylene-2,4-bis(trifluoroacetyl)-1-naphthylamine[10,21] was formed in 9% yield as a by-product and was separated from the mixture by chromatography using benzene as eluent .

3a: yield 98%; mp 98-99 °C (hexane/$CHCl_3$); IR (KBr) 1709 cm^{-1}; ^{1}H-NMR 9.43-9.15 (m, 2H, H-2, -7), 8.77-8.40 (m, 2H, H-5, -10), 7.86-7.57 (m, 2H, H-8, -9), 3.81 (q, 2H, J_{HF}=2, CH_2), 2.33 (s, 6H, CH_3); ^{13}C-NMR (CD_3COCD_3) 182.6 (q, J_{CF}=34.2), 156.6 (d), 153.9 (s), 135.0 (q, J_{CF}=30.5), 133.5 (s), 132.3 (s), 130.9 (d), 129.2 (d), 128.9 (s), 128.7 (d), 128.2 (s), 125.8 (d), 125.6 (d), 125.4 (q, J_{CF}=278.3), 119.6 (s), 117.4 (q, J=291.8), 59.6 (t of q, J_{CF}=3.7), 45.7 (q). Anal. Calcd for $C_{19}H_{14}N_2OF_6$: C, 57.01; H, 3.53; N, 7.00. Found: C, 56.78; H, 3.42; N, 7.05.

3b: yield 77%; mp 95-96 °C (hexane); IR (KBr) 1712 cm^{-1}; ^{1}H-NMR 9.29-8.96 (m, 2H, H-2, -7), 8.62-8.26 (m, 2H, H-5, -10), 7.71-7.43 (m, 2H, H-8, -9), 3.97 (q, J=2, 2H, CH_2), 2.77-2.41 (m, 4H, NCH_2), 1.92-1.66 (m, 4H, $NCH_2C\underline{H_2}$). Anal. Calcd for $C_{21}H_{16}N_2OF_6$: C, 59.16; H, 3.78; N, 6.57. Found: C, 59.08; H, 3.73; N, 6.48.

3c: yield 96%; mp 115-116 °C ($CHCl_3$/EtOAc); IR (KBr) 3320, 1717 cm^{-1}; ^{1}H-NMR 9.33-9.17 (m, 2H, H-2, -7), 8.77-8.43 (m, 2H, H-5, -10), 7.87-7.63 (m, 2H, H-8, -9), 4.07 (q, J=2, CH_2), 2.12-1.57 (br, 1H, NH), 1.23 (s, 9H, CH_3). Anal. Calcd for $C_{21}H_{18}N_2OF_6$: C, 58.88; H, 4.24; N, 6.54. Found: C, 58.82; H, 4.38; N, 6.46.

3d: yield 80%; mp 119-120 °C (hexane/$CHCl_3$); IR (KBr) 3428, 1718 cm^{-1}; ^{1}H-NMR 9.25-9.02 (m, 2H, H-2, -7), 8.69-8.33 (m, 2H, H-5, -10), 7.80-7.52 (m, 2H, H-8, -9), 7.27-6.41 (m, 5H, C_6H_5), 4.70 (br s, 2H, CH_2), 4.61-3.84 (br, 1H, NH). Anal. Calcd for $C_{23}H_{14}N_2OF_6$: C, 61.61; H, 3.15; N, 6.25. Found: C, 61.45; H, 3.00; N, 6.24.

Reaction of *N*-Propargyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (2) with Thiolates; General Procedure: A solution of sodium ethoxide was prepared by dissolving of sodium (23 mg, 1 mmol) in absolute EtOH (16 mL). To this was added the appropriate thiol (6 mmol) and the solution was

stirred for 15 min. To the clear solution was added **2** (747 mg, 2 mmol) and the reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and CH_2Cl_2 (50 ml) was added to the residue. The solution was washed with 1 N HCl (100 mL) and dried (Na_2SO_4). The solvent was evaporated and the crude product was chromatographed using hexane/benzene (2:3) for **3f**, and hexane/benzene (7:3) for **3e** and **3g** as eluent.

In the synthesis of **3g**, 3 mmol of sodium was used to 1 mmol of **2**.

3e: yield 100%; mp 95-96 ℃ (hexane/$CHCl_3$); IR (KBr) 1721 cm^{-1}; ^{1}H-NMR 9.33-8.95 (m, 2H, H-2, -7), 8.65-8.31 (m, 2H, H-5, -10), 7.80-7.52 (m, 2H, H-8, -9), 4.07 (q, J=2, 2H, CH_2), 2.56 (q, J=7, 2H, SCH_2), 1.27 (t, J=7, 3H, CH_3). Anal. Calcd for $C_{19}H_{13}NOF_6S$: C, 54.68; H, 3.14; N, 3.36. Found: C, 54.46; H, 2.92; N, 3.35.

3f: yield 72%; mp 94-95 ℃ (hexane/$CHCl_3$); IR (KBr) 1708 cm^{-1}; ^{1}H-NMR 9.20-8.91 (m, 1H, H-7), 8.76 (s, 1H, H-2), 8.54-8.23 (m, 2H, H-5, -10), 7.70-7.42 (m, 2H, H-8, -9), 7.26-6.94 (m, 5H, C_6H_5), 3.88 (q, J=2, CH_2), 3.68 (s, 2H, $SC\underline{H_2}Ph$). Anal. Calcd for $C_{24}H_{15}NOF_6S$: C, 60.12; H, 3.15; N, 2.92. Found: C, 60.05; H, 3.09; N, 2.75.

3g: yield 78%; mp 124-125 ℃ (hexane/$CHCl_3$); IR (KBr) 1711 cm^{-1}; ^{1}H-NMR 9.26-8.90 (m, 1H, H-7), 8.67-8.26 (m, 3H, H-2, -5, -10), 7.75-7.46 (m, 2H, H-8, -9), 7.40-7.04 (m, 5H, C_6H_5), 4.35 (q, J=2, 2H, CH_2). Anal. Calcd for $C_{23}H_{13}NOF_6S$: C, 59.36; H, 2.82; N, 3.01. Found: C, 59.09; H, 3.06; N, 3.01.

Reaction of *N*-Propargyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (2) with Alcoholates; with Sodium Methanolate: A solution of sodium methoxide was prepared by dissolving of sodium (23 mg, 1 mmol) in absolute MeOH (8 mL). To this solution was added **2** (373 mg, 1 mmol) and the solution was stirred at room temperature for 24 h. The solvent was evaporated, and CH_2Cl_2 (50 mL) was added to the residue. This solution was washed with 1 N HCl (100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was chromatographed using hexane/benzene (1:4) for **3h** (325 mg, 84%): mp 117-118 ℃ (hexane/$CHCl_3$); IR (KBr) 1717 cm^{-1}; ^{1}H-NMR 9.27-9.10 (m, 2H, H-2, -7), 8.63-8.38 (m, 2H, H-5, -10), 7.80-7.53 (m, 2H, H-8, -9), 4.78 (q, 2H, J=2, CH_2), 3.50 (s, 3H, OCH_3). Anal. Calcd for $C_{18}H_{11}NO_2F_6$: C, 55.82; H, 2.86; N, 3.62. Found: C, 55.86; H, 2.68; N, 3.76.

with Sodium Ethanolate: A solution of sodium ethoxide was prepared by dissolving of sodium (23 mg, 1 mmol) in absolute EtOH (16 mL). To this solution was added **2** (747 mg, 2 mmol) and the solution was stirred at room temperature for 24 h. The solvent was evaporated, and CH_2Cl_2 (50 mL) was added to the residue. This solution was washed with 1 N HCl (100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was chromatographed using hexane/benzene (1:4)

for **3i** (787 mg, 98%): mp 95-96 ℃ (hexane); IR (KBr) 1713 cm^{-1}; ^{1}H-NMR 9.27-9.05 (m, 2H, H-2, -7), 8.68-8.34 (m, 2H, H-5, -10), 7.83-7.53 (m, 2H, H-8, -9), 4.85 (q, 2H, J=2.4, CH_2), 3.67 (q, 2H, J=7, $OC\underline{H}_2CH_3$), 1.33 (t, 3H, J=7, CH_3). Anal. Calcd for $C_{19}H_{13}NO_2F_6$: C, 56.87; H, 3.27; N, 3.49. Found: C, 56.83; H, 3.24; N, 3.52.

with Sodium Phenolate: A solution of sodium ethoxide was prepared by dissolving of sodium (23 mg, 1 mmol) in absolute EtOH (8 mL). To this was added PhOH (6 mmol) and the solution was stirred for 15 min. To the clear solution was added **2** (373 mg, 1 mmol) and the solution was stirred at room temperature for 24 h. The solvent was evaporated, and CH_2Cl_2 (50 mL) was added to the residue. This solution was washed with 1 N HCl (100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was chromatographed using hexane/benzene (1:1) for **3j** (324 mg, 72%): mp 126-127 ℃ (hexane/$CHCl_3$); IR (KBr) 1717 cm^{-1}; ^{1}H-NMR 9.19-8.96 (m, 2H, H-2, -7), 8.65-8.24 (m, 2H, H-5, -10), 7.73-7.46 (m, 2H, H-8, -9), 7.37-6.72 (m, 5H, OC_6H_5), 5.30 (q, J=2, 2H, CH_2). Anal. Calcd for $C_{23}H_{13}NO_2F_6$: C, 61.48; H, 2.92; N, 3.12. Found: C, 61.30; H, 2.82; N, 3.10.

Synthesis of [(6-Trifluoroacetyl-4-trifluoromethylbenzo[*h*]quinolin-3-yl)methyl]trimethylammonium Iodide (4): To a solution of **3a** (1521 mg, 3.8 mmol) in $CHCl_3$ (15 mL) was added MeI (5394 mg, 38 mmol) and the solution was stirred at room temperature for 24 h. Removal of the solvent and excess MeI under reduced pressure gave **4** (2061 mg, 100%): dec 188 ℃ ($CHCl_3$/EtOAc); IR (KBr) 1718 cm^{-1}; ^{1}H-NMR 9.63 (s, 1H, H-2), 9.47-9.25 (m, 1H, H-7), 8.73-8.42 (m, 2H, H-5, -10), 7.97-7.67 (m, 2H, H-8, -9), 5.43-5.18 (m, 2H, CH_2), 3.32-3.28 (m, 9H, CH_3). Anal. Calcd for $C_{20}H_{17}N_2OF_6I$: C, 44.30; H, 3.16; N, 5.17. Found: C, 44.34; H, 3.08; N, 4.77.

Synthesis of 3-Benzylaminomethyl-6-trifluoroacetyl-4-trifluoromethylbenzo[*h*]quinoline (3k): To a solution of **4** (542 mg, 1 mmol) in PrCN (8 mL) were added benzylamine (129 mg, 1.2 mmol) and the solution was stirred at reflux temperature for 1 h. The solvent was evaporated and the crude product was chromatographed using benzene/EtOAc (19:1) as eluent to give **3k** (361 mg, 78%): mp 119-120 ℃ ($CHCl_3$/EtOAc); IR (KBr) 3385, 1719 cm^{-1}; ^{1}H-NMR 9.37-9.00 (m, 2H, H-2, -7), 8.77-8.33 (m, 2H, H-5, -10), 7.88-7.57 (m, 2H, H-8, -9), 8.23-7.03 (br, 1H, NH), 7.28 (s, 5H, C_6H_5), 4.12 (q, 2H, J=2, CH_2), 3.83 (s, 2H, $NC\underline{H}_2Ph$). Anal. Calcd for $C_{24}H_{16}N_2OF_6$: C, 62.34; H, 3.49; N, 6.06. Found: C, 62.14; H, 3,64; N, 6.11.

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23. In the present reaction, compound (**3a**) was also produced as a minor product in 18% yield. Separation of the **2** - **3a** mixtures was very easily accomplished by silica gel column chromatography.
24. Reactions of sodium phenolate were occasionally accompanied by the formation of small amounts of compound (**3i**) as a by-product.
25. Carbon-carbon triple bonds are more susceptible to nucleophilic addition catalyzed by bases than double bonds. For example, enol ethers can be produced by this type of reaction of alkynes with alcohols: J. March, 'Advanced Organic Chemistry, ' John Wiley & Sons, Inc., New York, 1992, pp.763-764.

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