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A CONCISE SYNTHESIS OF FLUORINE-CONTAINING BENZO[*h*]QUINOLINES AND BENZO[*h*]QUINOLONES BY SELECTIVE PYRIDINE AND PYRIDINONE RINGS FORMATION REACTIONS OF *N*-PROPARGYL-2,4-BIS(TRIFLUOROACETYL)-1-NAPHTHYLAMINE WITH VARIOUS ACTIVE METHYLENE COMPOUNDS

Etsuji Okada,[a,]* Dai Shibata,[b] Norikado Tsukushi,[b] Masato Dohura,[b] Norio Ota,[b] Satoru Adachi,[a] and Maurice Médebielle[c]

[a]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

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

[c]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

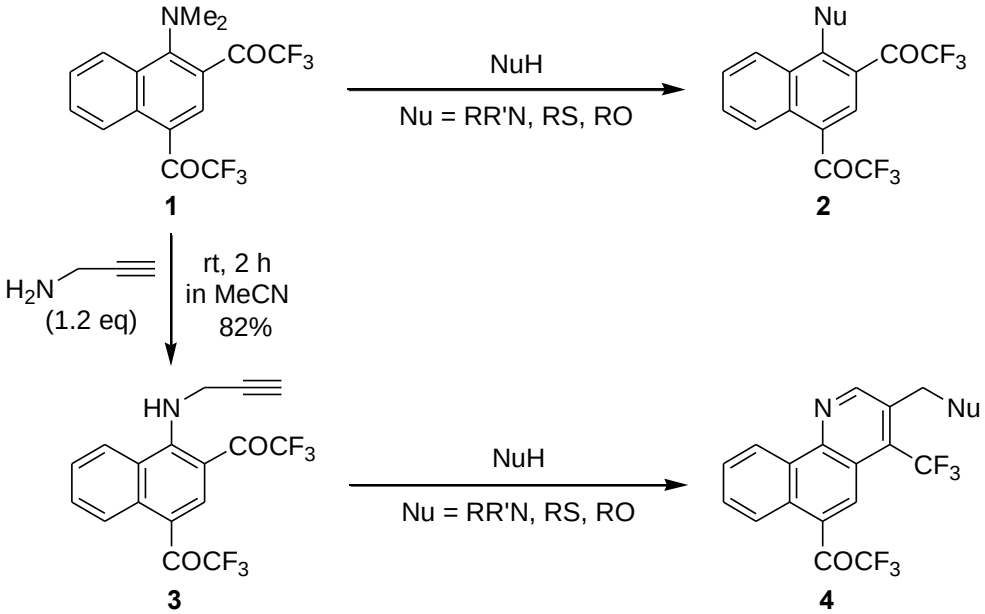
Abstract – *N*-Propargyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**3**) underwent nitrogen-containing heterocyclic ring-formation reactions with a variety of active methylene compounds in the presence of sodium alkoxides. This annulation reactions with dialkyl malonates were highly dependent on reaction temperature to give selectively the corresponding fluorine-containing benzo[*h*]quinolines (**5**) at high temperature and 1*H*-benzo[*h*]quinolin-2-ones (**7** and **8**) at low temperature. Furthermore, changing the electron-withdrawing groups of active methylene compounds led to alternation of the reactive site wherein the reagents attack first and to the formation of the different nitrogen-containing heterocyclic systems, pyridine (**9**), dihydropyridine (**11** and **13**) and pyridone (**12**).

INTRODUCTION

Benzo[*h*]quinoline and the related derivatives are valuable heterocyclic systems, constituting the structure

of many natural products, for example, fagaronine and nitidine, both isolated from trees belonging to the genus *Zanthoxylum* (Rutaceae).[1] And some benzo[*h*]quinoline derivatives have interesting biological activities such as antimicrobial agents,[2a,c,d] antitumor drugs[2b,e,f] and antimalarial activity.[4c] They are also known to be applicable to potent and selective 5α-reductase inhibitors.[3] Recently, the development of new methodologies for the synthesis of many kinds of fluorine-containing heterocycles has received much attention, since these compounds are now widely recognized as significant organic materials due to their interesting biological activities for their potential applications in medicinal and agricultural scientific fields.[4]

We have previously reported that *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**) undergoes novel aromatic nucleophilic substitution with various amines, thiols and alcohols to give the corresponding *N*-*N*, *N*-*S*, and *N*-*O* exchanged products (**2**) in excellent yields, respectively (Scheme 1).[5] Furthermore, we succeeded in applying this type of aromatic nucleophilic substitution and the subsequent cyclizations to the simple syntheses of various naphthalene-fused pyrroles, pyrazoles, quinolines, thiophenes, pyrans, thiopyrans, and diazepines bearing CF_3 groups.[6] In the course of investigating the synthesis of fluorine-containing heterocycles, it was found that various *N*-, *S*- and *O*-nucleophiles attack selectively the terminal acetylenic carbon of *N*-propargyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**3**), which was prepared by *N*-*N* exchange reaction of **1** with propargylamine, and mediate a novel pyridine-ring formation reaction to give the corresponding benzo[*h*]quinolines (**4**) having a CF_3 group at the 4-position in excellent yields (Scheme 1).[7]



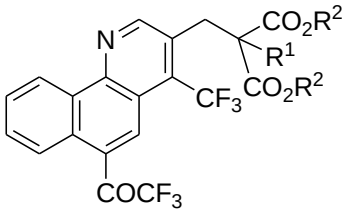
Scheme 1

In this situation, we have very recently reported that a facile and selective synthetic method for fluorine-containing benzo[*h*]quinolines (**5** and **6**) and 1*H*-benzo[*h*]quinolones (**7** and **8**) by the ring closure reaction of **3** with *C*-nucleophiles, dialkyl malonates in the presence of sodium alkoxides, which was very dependent on reaction temperature.[8]

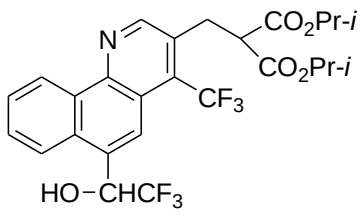
Herein we report a full account of our systematic studies on this type of cyclization reaction including a detailed investigation and an extension of the remarkable reactivity of **3** with other *C*-nucleophiles, β-diketones, β-ketoesters, methyl cyanoacetate, and malononitrile. The present reactions provide the facile and workable methods for construction of diverse CF_3-containing benzo[*h*]quinolines and benzo[*h*]quinolones, which are not easily obtained by other methods.

RESULTS AND DISCUSSION

We first examined the pyridine-ring formation reaction of **3** with dialkyl malonates (Figure 1) and the results are summarized in Table 1. The reaction of **3** with dimethyl malonate (3 equiv) proceeded cleanly in the presence of sodium methoxide (1 equiv) in refluxing methanol to afford the corresponding fluorine-containing benzo[*h*]quinoline (**5a**) having a di(methoxycarbonyl)ethyl group at the 3-position in 83% yield (entry 1). The same type of reaction with diethyl malonate in ethanol was completed within 5 min at reflux temperature to give the desired benzo[*h*]quinoline (**5b**) in 77% yield (entry 4). Under the almost same conditions, reaction of **3** with diisopropyl malonate provided a mixture of benzo[*h*]quinoline (**5c**) and its reduced product (**6**) in 43% and 44% yields, respectively (entry 7). Separation of the mixtures into **5c** and **6** was easily performed by silica gel column chromatography. In the cases of less



5a-e



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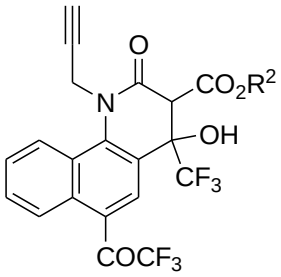
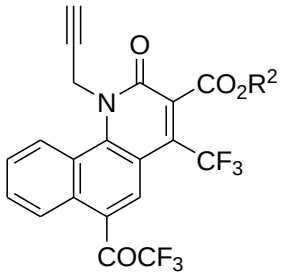


7a-c



8a-c

5,**7**,**8**	R^1	R^2
a	H	Me
b	H	Et
c	H	*i*-Pr
d	H	*t*-Bu
e	Me	Et

Figure 1

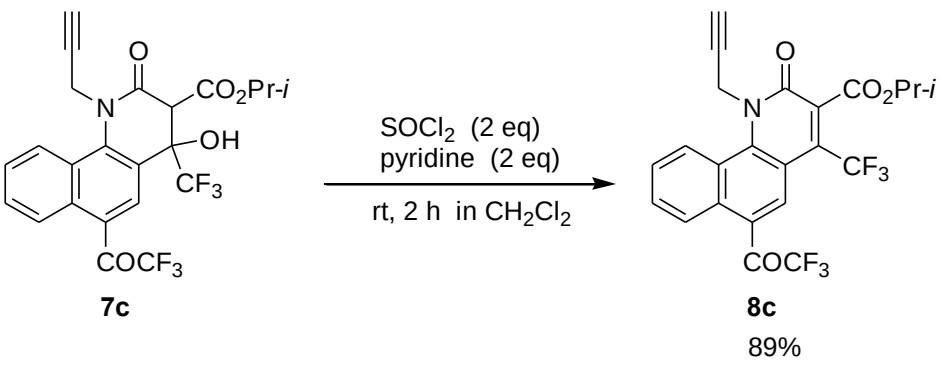
Table 1 Reaction of *N*-Propargyl-2,4-bis(trifluoroacetyl)-1-naphthylamine **3** with Dialkyl Malonates [$R^1CH(CO_2R^2)_2$]

Entry	$R^1CH(CO_2R^2)_2$			Na	Solvent	Temp.	Time	Product	Yield[a)]
	R^1	R^2	(eq)	(eq)		(°C)	(h)		(%)
1	H	Me	3	1	MeOH	reflux (65)	0.5	**5a**	83
2	H	Me	3	1	MeOH	30	48	**5a** / **8a**	45 / 44
3	H	Me	5	2	MeOH	0	72	**7a** / **8a**	13 / 11[b)]
4	H	Et	3	1	EtOH	reflux (78)	5 min	**5b**	77
5	H	Et	3	1	EtOH	30	18	**5b** / **8b**	46 / 46
6	H	Et	5	2	EtOH	0	72	**7b** / **8b**	42 / 51
7	H	*i*-Pr	3	1	*i*-PrOH	reflux (82)	5 min	**5c** / **6**	43 / 44
8	H	*i*-Pr	3	1	*i*-PrOH	30	2	**5c** / **7c**	35 / 53
9	H	*i*-Pr	5	2	*i*-PrOH	-20	72	**7c**	100
10	H	*t*-Bu	3	1	*t*-BuOH	30	18	**5d**	75
11	Me	Et	3	1	EtOH	30	24	**5e**	95

a) Isolated yields.
b) 75% of substrate **3** was recovered.

reactive di-*t*-butyl malonate and diethyl methylmalonate, heating at lower temperature (30 °C) and for longer time (18 h) was required for completion of the reaction without decomposition products and afforded benzo[*h*]quinolines (**5d** and **5e**) in 75% and 95% yields, respectively (entries 10 and 11).

It is noteworthy that as the reaction temperature was lowered, the reaction pathway changed dramatically (entries 3, 6, and 9). Reaction of **3** with dimethyl malonate at 0 °C yielded 4-hydroxy-3,4-dihydro-1*H*-benzo[*h*]quinolin-2-one (**7a**) and its dehydrated product, 1*H*-benzo[*h*]quinolin-2-one (**8a**), in 13% and 11% yields, respectively, accompanied a recovery of 75% substrate without any formation of benzo[*h*]quinoline (**5b**) (entry 3). In the same way, **3** reacted with diethyl malonate to afford **7b** and **8b** in 42% and 51% yields, respectively (entry 6). Moreover **3** underwent the lactam ring formation with diisopropyl malonate at -20 °C to give exclusively 4-hydroxy-3,4-dihydro-1*H*-benzo[*h*]quinolin-2-one (**7c**) quantitatively (entry 9). When the reactions were conducted at 30 °C, the mixture of benzo[*h*]quinolines (**5**) and benzo[*h*]quinolones (**7** or **8**) were obtained expectedly in high combined yields (entries 2, 5, and 8).

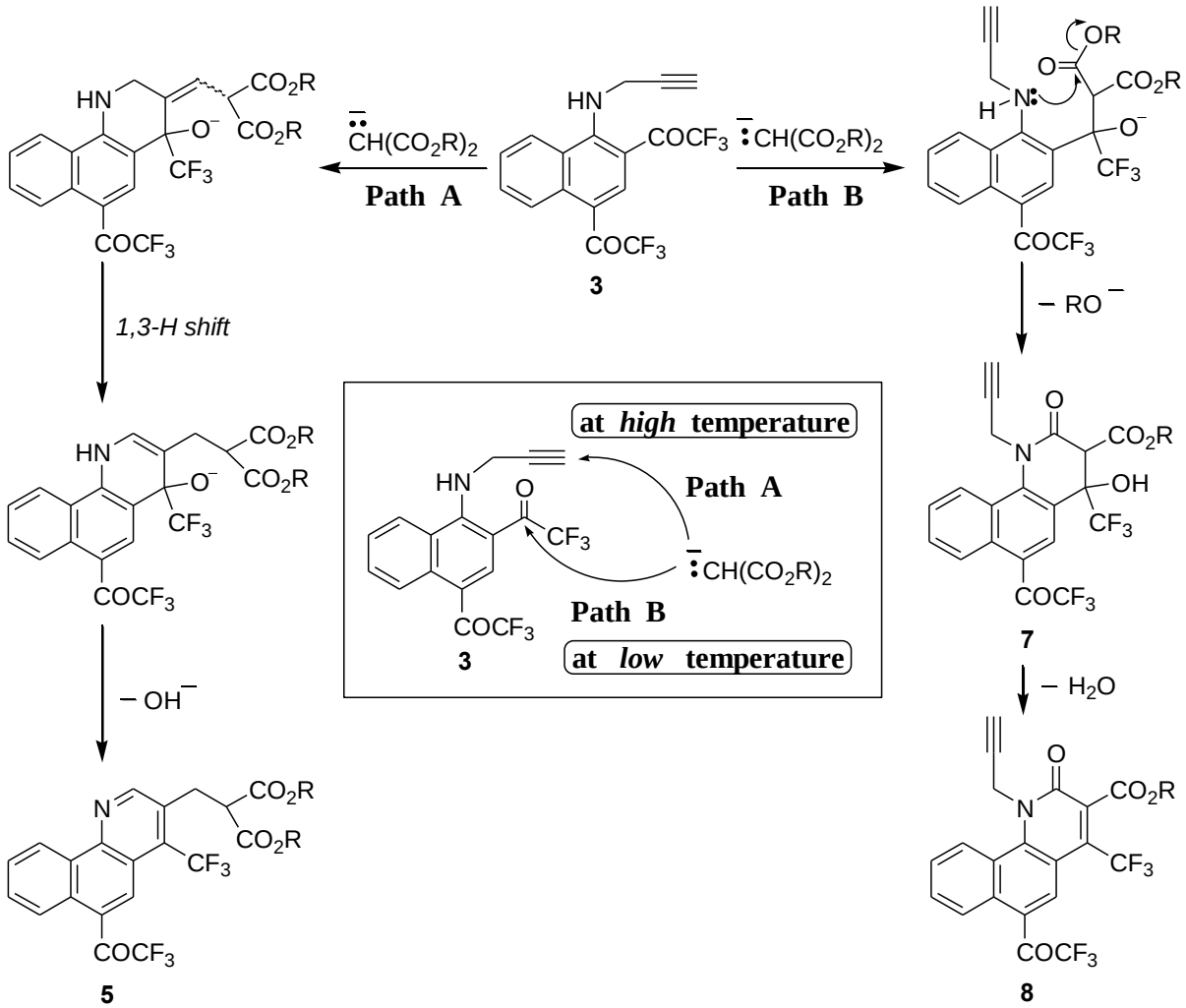


7c **8c** 89%

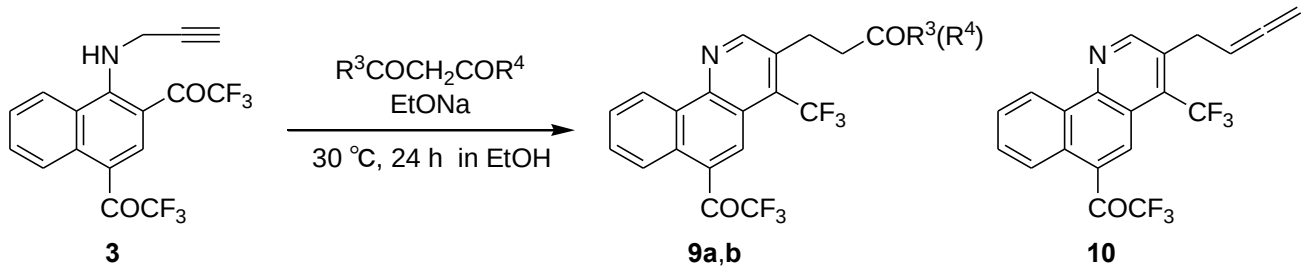
Scheme 2

Di(isopropoxycarbonyl) derivative (**7c**) was hard to be dehydrated compared to di(methoxycarbonyl) derivative (**7a**) and di(ethoxycarbonyl) derivative (**7b**). Therefore, conversion of **7c** into the corresponding dehydrated product (**8c**) was achieved by formal dehydration, namely *HO-Cl* exchange and subsequent dehydrochlorination, with the use of thionyl chloride in the presence of pyridine (Scheme 2).

Possible mechanistic pathways for the formation of benzo[*h*]quinolines (**5**) and 1*H*-benzo[*h*]quinolin-2-ones (**7** and **8**) are depicted in Scheme 3. At *high* temperature, both the addition of enolates (carbanions) from dialkyl malonates to the terminal acetylenic carbon and the attack of carbonyl carbon onto the internal acetylenic carbon occur concertedly to give the corresponding cyclization product, which leads to **5** via 1,3-H shift and the subsequent departure of hydroxide ion (Path A). On the other hand, at *low* temperature, the addition of enolates takes place on the carbonyl carbon of trifluoroacetyl group at the 2-position, followed by the intramolecular ester-amide exchange reaction (lactam ring formation) to afford **7** leading to **8** by dehydration (Path B). It is not certain at present why the interesting temperature-dependent chemoselectivity was clearly observed in this system. Further studies are underway to elucidate definitely the mechanism.



Scheme 3



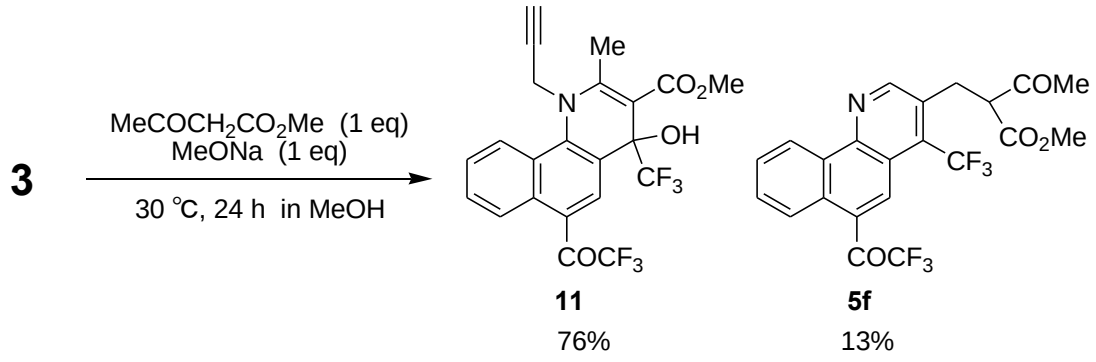
Scheme 4

Table 2 Reaction of *N*-Propargyl-2,4-bis(trifluoroacetyl)-1-naphthylamine **3** with β-Diketones

Entry	$R^3COCH_2COR^4$			Na	Product	Yield[a)]
	R^3	R^4	(eq)	(eq)		(%)
1	Me	Me	1	1	**9a**	75
2	Me	Me	3	0.25	**10**	30[b)]
3	Ph	Ph	1	1	**9b**	87[c)]
4	Me	Ph	1	1	**9a** / **9b**	27 / 59[d)]

a) Isolated yields.
b) 20% of substrate **3** was recovered.
c) Ether **4** (Nu = OEt in Scheme 1) was obtained in 13%.
d) Ether **4** (Nu = OEt in Scheme 1) was obtained in 11%.

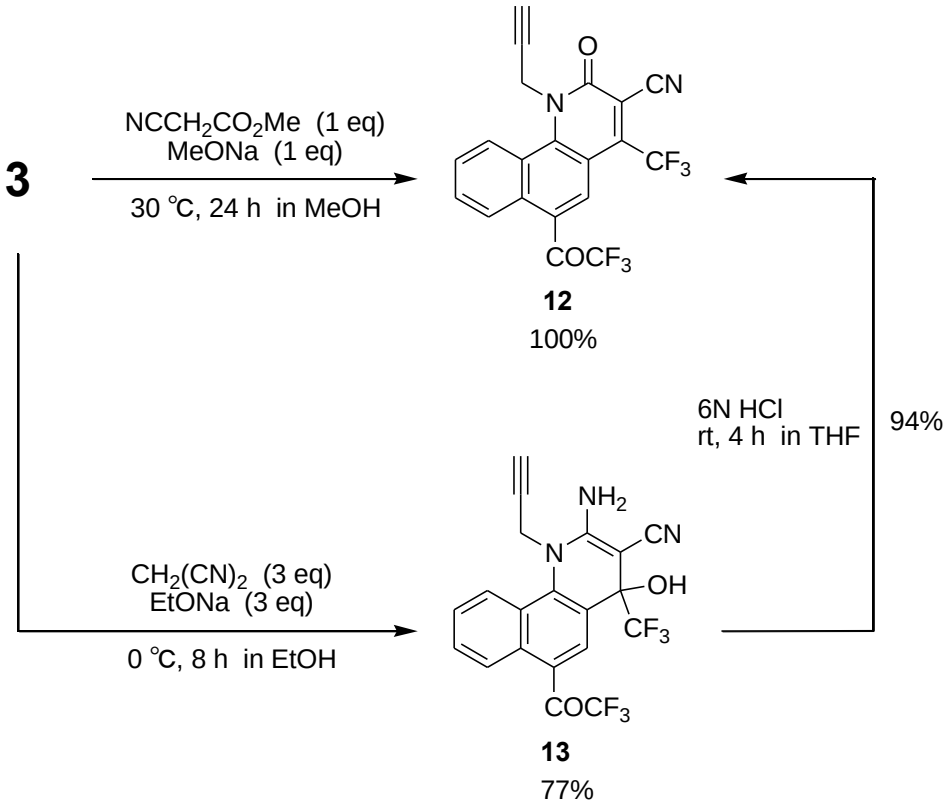
Next, we attempted to carry out the present cyclization using β-diketones (Scheme 4, Table 2). The pyridine-ring formation reaction of **3** with acetyl acetone (1 equiv) and the subsequent deacetylation took place cleanly in the presence of sodium ethoxide (1 equiv) in ethanol at 30 °C within 24 h to afford the novel fluorine-containing 3-acetylethylbenzo[*h*]quinoline (**9a**) having a 3-oxobutyl group at the 3-position in 75% yield (entry 1). Interestingly, when we increased the amount of acetylacetone (3 equiv) and decreased that of sodium ethoxide (0.25 equiv), allene derivative (**10**) was obtained as a major product (entry 2). The mechanism of the generation of **10** is not yet clarified. Dibenzoylmethane also underwent the pyridine-ring formation and the subsequent debenzoylation under the similar conditions for



Scheme 5

acetylacetone (entry 1), to give the corresponding benzoylethylbenzo[*h*]quinoline (**9b**) (entry 3). Besides, in the reaction with unsymmetrical β-diketones, benzoylacetone, both **9a** (27%) and **9b** (59%) were produced (entry 4).

Furthermore, the present reactions were applied to other active methylene compounds such as β-ketoesters, methyl cyanoacetate, and malononitrile. The cyclization of **3** with methyl acetoacetate proceeded easily in the presence of sodium methoxide in methanol to produce 1-propargyl-1,4-dihydrobenzo[*h*]quinoline (**11**) as a major product together with benzo[*h*]quinoline (**5f**) (Scheme 5). Treatment of methyl cyanoacetate with **3** in the presence of sodium methoxide at 30 °C resulted in quantitative conversion to 3-cyano-1-propargylbenzo[*h*]quinolone (**12**) (Scheme 6). When we conducted the reaction of **3** with malononitrile in the presence of sodium ethoxide at 0 °C, the cyclization underwent through the similar reaction route to afford 2-amino-3-cyano-1-propargyl-1,4-dihydrobenzo[*h*]quinoline (**13**), which was successively converted to **12** by the hydrolysis using an aqueous solution of 6N HCl.



Scheme 6

In conclusion, we succeeded in extending the ring formation reactions of **3** with *N*-, *S*-, and *O*-nucleophiles to those with *C*-nucleophiles such as various active methylene compounds, dialkyl malonates, β-diketones, β-ketoesters, methyl cyanoacetate, and malononitrile, and in providing an

efficient and selective synthetic method for fluorine-containing benzo[*h*]quinolines and 1*H*-benzo[*h*]quinolin-2-ones, which are not easily accessible by other methods. We found the highly temperature-dependent alternation of the reactive site wherein the reagents attack first on the reaction of **3** with dialkyl malonates. Also, we clarified that the similar chemoselectivity appeared by changing the electron-withdrawing groups of active methylene compounds, and led to the formation of the different nitrogen-containing heterocyclic systems, pyridine and pyridone. For detail, the reaction of **3** with β-diketones proceeded through the Path A, and that with β-ketoesters, methyl cyanoacetate, and malononitrile underwent through the Path B selectively.

EXPERIMENTAL

Mps were determined on an electrothermal digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on JEOL PMX 60SI and Bruker AVANCE500 instruments using TMS as an internal standard. ^{13}C NMR spectra were obtained with a JEOL FX90Q spectrometer. IR spectra were taken with JASCO A-302 and PerkinElmer Spectrum ONE spectrophotometers. Microanalyses were taken with a YANACO CHN-Coder MT-5 analyzer.

Reaction of 3 with Active Methylene Compounds; General Procedure

Method A: At High Temperature

Sodium (3 mmol) and active methylene compounds (9 mmol) were added to alcohols (24 mL) and the mixture was stirred at room temperature for 15 min. To the solution was added **3**[5a] (1.12 g, 3 mmol) and then it was stirred for 5-30 min at reflux temperature. The reaction was quenched with 1N HCl and the solvent was removed under reduced pressure. The mixture was extracted with EtOAc (200 mL), washed with water (200 mL), and dried over Na_2SO_4. Evaporation of the solvent gave the crude mixture which was submitted to column chromatography on silica gel eluting with *n*-hexane/EtOAc (49:1 - 4:1) to give **5a-c**, **6**.

Method B: At Low Temperature

Sodium (0.75 - 9 mmol) and active methylene compounds (3 - 15 mmol) were added to alcohols (24 mL) and the mixture was stirred at room temperature for 15 min. To the solution was added **3** (1.12 g, 3 mmol) and then it was stirred at -20 - 30 °C for 2 - 72 h. The reaction was quenched with 1N HCl and the solvent was removed under reduced pressure. The mixture was extracted with EtOAc (200 mL), washed with water (200 mL), and dried over Na_2SO_4. Evaporation of the solvent gave the crude mixture which was submitted to column chromatography on silica gel eluting with *n*-hexane/EtOAc (49:1 - 4:1) to give **5a-e**, **7**, **8a**,**b**, **9**-**10** and with benzene/EtOAc (1:0 - 1:1) to give **5f**, **11**, **13**. In the case of methyl cyanoacetate, evaporation of the solvent gave practically pure **12**. In the case of malononitorile,

quenched with sat. NH_4Cl instead of 1N HCl.

Dimethyl 2-(6-(2,2,2-trifluoroacetyl)-4-trifluoromethylbenzo[*h*]quinolin-3-ylmethyl)malonate (5a): mp 117-118 °C (*n*-C_6H_{14}/$CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 9.31 (dd, *J* = 4.0, 7.0 Hz, 1H, H-7 or 10), 9.05 (s, 1H, H-2), 8.72 (br s, 1H, H-5), 8.55 (dd, *J* = 4.0, 7.0 Hz, 1H, H-10 or 7), 7.92-7.61 (m, 2H, H-8, H-9), 3.90-3.60 (m, 3H, CH_2CH), 3.74 (s, 6H, OCH_3); IR (KBr): 1751, 1738, 1710 cm^{-1}. Anal. Calcd for $C_{22}H_{15}F_6NO_5$: C, 54.22; H, 3.10; N, 2.87. Found: C, 54.49; H, 2.83; N, 2.87.

Diethyl 2-(6-(2,2,2-trifluoroacetyl)-4-trifluoromethylbenzo[*h*]quinolin-3-ylmethyl)malonate (5b): mp 83-84 °C (*n*-C_6H_{14}/$CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 9.34 (dd, *J* = 4.0, 7.0 Hz, 1H, H-7 or 10), 9.07 (s, 1H, H-2), 8.74 (br s, 1H, H-5), 8.56 (dd, *J* = 4.0, 7.0 Hz, 1H, H-10 or 7), 7.92-7.62 (m, 2H, H-8, H-9), 4.20 (q, *J* = 7.0 Hz, 4H, $C\underline{H}_2CH_3$), 3.80-3.65 (m, 3H, CH_2CH), 1.21 (t, *J* = 7.0 Hz, 6H, $CH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$): δ 182.1 (q, J_{CF} = 34.2 Hz), 168.3, 156.5, 148.0, 133.2 (q, J_{CF} = 29.3 Hz), 131.5, 130.7, 130.4, 128.9, 128.5, 128.2, 127.6, 125.3, 124.9, 124.6 (q, J_{CF} = 277.9 Hz), 119.2, 116.7 (q, J_{CF} = 293.0 Hz), 62.2, 53.5, 31.1, 14.1; IR (KBr): 1733, 1718, 1710 cm^{-1}. Anal. Calcd for $C_{24}H_{19}F_6NO_5$: C, 55.93; H, 3.72; N, 2.72. Found: C, 55.86; H, 3.92; N, 2.59.

Diisopropyl 2-(6-(2,2,2-trifluoroacetyl)-4-trifluoromethylbenzo[*h*]quinolin-3-ylmethyl)malonate (5c): mp 111-112 °C (*n*-C_6H_{14}/$CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 9.22 (dd, *J* = 4.0, 7.0 Hz, 1H, H-7 or 10), 8.99 (s, 1H, H-2), 8.66 (br s, 1H, H-5), 8.48 (dd, *J* = 4.0, 7.0 Hz, 1H, H-10 or 7), 7.83-7.55 (m, 2H, H-8, H-9), 5.01 (hp, *J* = 6.0 Hz, 2H, OCH), 3.81-3.50 (m, 3H, CH_2CH), 1.25 (d, *J* = 6.0 Hz, 6H, CH_3), 1.17 (d, *J* = 6.0 Hz, 6H, CH_3); IR (KBr): 1749, 1727, 1714 cm^{-1}. Anal. Calcd for $C_{26}H_{23}F_6NO_5$: C, 57.46; H, 4.27; N, 2.58. Found: C, 57.37; H, 4.35; N, 2.59.

Di-*tert*-butyl 2-(6-(2,2,2-trifluoroacetyl)-4-trifluoromethylbenzo[*h*]quinolin-3-ylmethyl)malonate (5d): mp 106-107 °C (*n*-C_6H_{14}); ^{1}H NMR ($CDCl_3$): δ 9.30 (dd, *J* = 4.0, 7.0 Hz, 1H, H-7 or 10), 9.08 (s, 1H, H-2), 8.75 (br s, 1H, H-5), 8.55 (dd, *J* = 4.0, 7.0 Hz, 1H, H-10 or 7), 7.88-7.60 (m, 2H, H-8, H-9), 3.76-3.47 (m, 3H, CH_2CH), 1.41 (s, 18H, CH_3); IR (KBr): 1737, 1716, 1706 cm^{-1}. Anal. Calcd for $C_{28}H_{27}F_6NO_5$: C, 58.84; H, 4.76; N, 2.45. Found: C, 59.05; H, 4.72; N, 2.45.

Diethyl 2-methyl-2-(6-(2,2,2-trifluoroacetyl)-4-trifluoromethylbenzo[*h*]quinolin-3-ylmethyl)-malonate (5e): mp 90-91 °C (*n*-C_6H_{14}/EtOAc); ^{1}H NMR ($CDCl_3$): δ 9.22 (dd, *J* = 4.0, 7.0 Hz, 1H, H-7 or 10), 8.94 (s, 1H, H-2), 8.69 (br s, 1H, H-5), 8.50 (dd, *J* = 4.0, 7.0 Hz, 1H, H-10 or 7), 7.84-7.54 (m, 2H, H-8, H-9), 4.21 (q, *J* = 7.0 Hz, 4H, $C\underline{H}_2CH_3$), 3.79 (q, J_{HF} = 2.0 Hz, 2H, CH_2), 1.41 (s, 3H, CH_3), 1.24 (t,

J = 7.0 Hz, 6H, $CH_2C\underline{H}_3$); IR (KBr): 1732, 1717, 1704 cm^{-1}. Anal. Calcd for $C_{25}H_{21}F_6NO_5$: C, 56.72; H, 4.00; N, 2.65. Found: C, 56.70; H, 4.07; N, 2.58.

Diisopropyl 2-(6-(2,2,2-trifluoro-1-hydroxyethyl)-4-trifluoromethylbenzo[*h*]quinolin-3-ylmethyl)-malonate (6): mp 107-108 °C (*n*-C_6H_{14}/EtOAc); ^{1}H NMR ($CDCl_3$): δ 9.23 (dd, *J* = 4.0, 7.0 Hz, 1H, H-7 or 10), 8.91 (s, 1H, H-2), 8.35 (br s, 1H, H-5), 8.17-7.48 (m, 3H, H-10 or 7, H-8, H-9), 5.88 (q, J_{HF} = 7.0 Hz, 1H, $CHCF_3$), 5.03 (hp, *J* = 6.0 Hz, 2H, OCH), 4.33-3.21 (br, 1H, OH), 3.72-3.49 (m, 3H, CH_2CH), 1.23 (d, *J* = 6.0 Hz, 6H, CH_3), 1.15 (d, *J* = 6.0 Hz, 6H, CH_3); IR (KBr): 3420, 1745, 1723 cm^{-1}. Anal. Calcd for $C_{26}H_{25}F_6NO_5$: C, 57.25; H, 4.62; N, 2.57. Found: C, 56.96; H, 4.73; N, 2.49.

Methyl 4-hydroxy-2-oxo-1-(prop-2-ynyl)-6-(2,2,2-trifluoroacetyl)-4-trifluoromethyl-1,2,3,4-tetrahydrobenzo[*h*]quinoline-3-carboxylate (7a): mp 183-184 °C (*n*-C_6H_{14}); ^{1}H NMR ($CDCl_3$): δ 8.95-8.68 (m, 1H, H-7), 8.45-8.23 (m, 2H, H-5, H-10), 7.89-7.48 (m, 2H, H-8, H-9), 5.36 (br s, 1H, OH), 4.48 (dq_{AB}, *J* = 2.5, 17.0 Hz, Δδ = 0.26 ppm, 2H, CH_2), 4.17 (s, 1H, CH), 3.65 (s, 3H, OCH_3), 2.44 (t, *J* = 2.5 Hz, 1H, C≡CH); IR (KBr): 3330, 3270, 2120, 1741, 1734, 1685 cm^{-1}. Anal. Calcd for $C_{21}H_{13}F_6NO_5$: C, 53.29; H, 2.77; N, 2.96. Found: C, 53.17; H, 2.85; N, 2.99.

Ethyl 4-hydroxy-2-oxo-1-(prop-2-ynyl)-6-(2,2,2-trifluoroacetyl)-4-trifluoromethyl-1,2,3,4-tetrahydrobenzo[*h*]quinoline-3-carboxylate (7b): mp 175-176 °C (*n*-C_6H_{14}); ^{1}H NMR ($CDCl_3$): δ 9.16-8.82 (m, 1H, H-7), 8.71-8.45 (m, 2H, H-5, H-10), 7.97-7.62 (m, 2H, H-8, H-9), 5.56 (br s, 1H, OH), 4.56 (dq_{AB}, *J* = 2.5, 17.0 Hz, Δδ = 0.30 ppm, 2H, CH_2), 4.21 (s, 1H, CH), 4.15 (q, *J* = 7.0 Hz, 2H, $C\underline{H}_2CH_3$), 2.52 (t, *J* = 2.5 Hz, 1H, C≡CH), 1.05 (t, *J* = 7.0 Hz, 3H, $CH_2C\underline{H}_3$); IR (KBr): 3320, 3260, 2116, 1743, 1734, 1683 cm^{-1}. Anal. Calcd for $C_{22}H_{15}F_6NO_5$: C, 54.22; H, 3.10; N, 2.87. Found: C, 54.16; H, 3.14; N, 2.89.

Isopropyl 4-hydroxy-2-oxo-1-(prop-2-ynyl)-6-(2,2,2-trifluoroacetyl)-4-trifluoromethyl-1,2,3,4-tetrahydrobenzo[*h*]quinoline-3-carboxylate (7c): mp 174-175 °C ($CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 9.04-8.77 (m, 1H, H-7), 8.57-8.32 (m, 2H, H-5, H-10), 7.93-7.64 (m, 2H, H-8, H-9), 5.60 (br s, 1H, OH), 4.93 (hp, *J* = 6.0 Hz, 1H, OCH), 4.51 (dq_{AB}, *J* = 2.5, 17.0 Hz, Δδ = 0.34 ppm, 2H, CH_2), 4.13 (s, 1H, CH), 2.50 (t, *J* = 2.5 Hz, 1H, C≡CH), 1.18 (d, *J* = 6.0 Hz, 3H, CH_3), 0.82 (d, *J* = 6.0 Hz, 3H, CH_3); IR (KBr): 3345, 3288, 2133, 1746, 1708, 1688 cm^{-1}. Anal. Calcd for $C_{23}H_{17}F_6NO_5$: C, 55.10; H, 3.42; N, 2.79. Found: C, 55.21; H, 3.43; N, 2.67.

Methyl 2-oxo-1-(prop-2-ynyl)-6-(2,2,2-trifluoroacetyl)-4-trifluoromethyl-1,2-dihydrobenzo[*h*]-

quinoline-3-carboxylate (8a): mp 210-211 °C (*n*-C_6H_{14}/EtOAc); ^{1}H NMR ($CDCl_3$): δ 9.13-8.79 (m, 2H, H-7, H-10), 8.59 (br s, 1H, H-5), 8.08-7.68 (m, 2H, H-8, H-9), 4.99 (d, *J* = 2.5 Hz, 2H, CH_2), 4.01 (s, 3H, OCH_3), 2.71 (t, *J* = 2.5 Hz, 1H, C≡CH); IR (KBr): 3300, 2108, 1740, 1730, 1718 cm^{-1}. Anal. Calcd for $C_{21}H_{11}F_6NO_4$: C, 55.40; H, 2.44; N, 3.08. Found: C, 55.27; H, 2.69; N, 2.96.

Ethyl 2-oxo-1-(prop-2-ynyl)-6-(2,2,2-trifluoroacetyl)-4-trifluoromethyl-1,2-dihydrobenzo[*h*]-quinoline-3-carboxylate (8b): mp 180-181 °C (*n*-C_6H_{14}/EtOAc); ^{1}H NMR ($CDCl_3$): δ 9.05-8.68 (m, 2H, H-7, H-10), 8.51 (br s, 1H, H-5), 8.00-7.59 (m, 2H, H-8, H-9), 4.94 (d, *J* = 2.5 Hz, 2H, CH_2), 4.46 (q, *J* = 7.0 Hz, 2H, $C\underline{H}_2CH_3$), 2.72 (t, *J* = 2.5 Hz, 1H, C≡CH), 1.41 (t, *J* = 7.0 Hz, 3H, $CH_2C\underline{H}_3$); IR (KBr): 3290, 2108, 1745, 1738, 1696 cm^{-1}. Anal. Calcd for $C_{22}H_{13}F_6NO_4$: C, 56.30; H, 2.79; N, 2.98. Found: C, 56.39; H, 2.99; N, 2.93.

Isopropyl 2-oxo-1-(prop-2-ynyl)-6-(2,2,2-trifluoroacetyl)-4-trifluoromethyl-1,2-dihydrobenzo[*h*]-quinoline-3-carboxylate (8c): mp 189-190 °C (*n*-C_6H_{14}/EtOAc); ^{1}H NMR ($CDCl_3$): δ 9.00-8.76 (m, 2H, H-7, H-10), 8.53 (br s, 1H, H-5), 7.95-7.59 (m, 2H, H-8, H-9), 5.32 (hp, *J* = 6.0 Hz, 1H, OCH), 4.93 (d, *J* = 2.5 Hz, 2H, CH_2), 2.68 (t, *J* = 2.5 Hz, 1H, C≡CH), 1.40 (d, *J* = 6.0 Hz, 6H, CH_3); IR (KBr): 3248, 2148, 1735, 1713, 1698 cm^{-1}. Anal. Calcd for $C_{23}H_{15}F_6NO_4$: C, 57.15; H, 3.13; N, 2.90. Found: C, 57.01; H, 3.22; N, 2.81.

Dehydration of 7c into 8c

To a solution of **7c** (1.00 g, 2 mmol) and pyridine (0.32 g, 4 mmol) in CH_2Cl_2 (16 mL) was added dropwise thionyl chloride (0.48 g, 4 mmol) with cooling and the stirring was continued at room temperature for 2 h. The mixture was extracted with CH_2Cl_2 (50 mL), washed with sat. Na_2CO_3 (100 mL), with 1N HCl (100 mL), and dried over Na_2SO_4. Evaporation of the solvent gave the practically pure **8c** (0.86 g, 1.78 mmol, 89%).

4-(6-(2,2,2-Trifluoroacetyl)-4-trifluoromethylbenzo[*h*]quinolin-3-yl)butan-2-one (9a): mp 141-142 °C (*n*-C_6H_{14}/$CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 9.30 (dd, *J* = 4.0, 7.0 Hz, 1H, H-7 or 10), 9.02 (s, 1H, H-2), 8.70 (br s, 1H, H-5), 8.52 (dd, *J* = 4.0, 7.0 Hz, 1H, H-10 or 7), 7.93-7.53 (m, 2H, H-8, H-9), 3.56-3.15 (m, 2H, CH_2), 2.98-2.72 (m, 2H, CH_2CO), 2.18 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 205.9, 182.4 (q, J_{CF} = 34.2 Hz), 156.2, 147.7, 134.0, 132.6 (q, J_{CF} = 30.5 Hz), 131.8, 130.3, 128.9, 128.6, 128.0, 127.9, 125.3, 124.9, 124.5 (q, J_{CF} = 277.1 Hz), 119.3, 116.5 (q, J_{CF} = 293.0 Hz), 45.0, 29.8, 26.2; IR (KBr): 1729, 1715 cm^{-1}. Anal. Calcd for $C_{20}H_{13}F_6NO_2$: C, 58.12; H, 3.17; N, 3.39. Found: C, 58.40; H, 2.96; N, 3.32.

1-Phenyl-3-(6-(2,2,2-trifluoroacetyl)-4-trifluoromethylbenzo[*h*]quinolin-3-yl)propan-1-one (9b): mp 144-145 °C (*n*-C_6H_{14}/EtOAc); ^{1}H NMR ($CDCl_3$): δ 9.24 (dd, *J* = 4.0, 7.0 Hz, 1H, H-7 or 10), 9.07 (s, 1H, H-2), 8.67 (br s, 1H, H-5), 8.50 (dd, *J* = 4.0, 7.0 Hz, 1H, H-10 or 7), 8.00-7.24 (m, 7H, H-8, H-9, Ph), 3.69-3.26 (m, 4H, CH_2); IR (KBr): 1706, 1680 cm^{-1}. Anal. Calcd for $C_{25}H_{15}F_6NO_2$: C, 63.16; H, 3.18; N, 2.95. Found: C, 63.23; H, 3.42; N, 2.87.

1-(3-(Buta-2,3-dienyl)-4-trifluoromethylbenzo[*h*]quinolin-6-yl)-2,2,2-trifluoroethanone (10): mp 82-83 °C (*n*-C_6H_{14}); ^{1}H NMR ($CDCl_3$): δ 9.08 (dd, *J* = 4.0, 7.0 Hz, 1H, H-7 or 10), 8.45-8.23 (m, 2H, H-2, H-5), 7.66-7.37 (m, 3H, H-10 or 7, H-8, H-9), 5.70-5.23 (m, 1H, CH), 4.80-4.61 (m, 2H, C=CH_2), 3.85-3.63 (m, 2H, CH_2); IR (KBr): 1953, 1712 cm^{-1}. Anal. Calcd for $C_{20}H_{11}F_6NO$: C, 60.77; H, 2.80; N, 3.54. Found: C, 61.14; H, 2.47; N, 3.51.

Methyl 3-oxo-2-(6-(2,2,2-trifluoroacetyl)-4-trifluoromethylbenzo[*h*]quinolin-3-ylmethyl)butanoate (5f): mp 103-104 °C (*n*-C_6H_{14}/$CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 9.25 (dd, *J* = 4.0, 7.0 Hz, 1H, H-7 or 10), 9.00 (s, 1H, H-2), 8.64 (br s, 1H, H-5), 8.48 (dd, *J* = 4.0, 7.0 Hz, 1H, H-10 or 7), 7.85-7.56 (m, 2H, H-8, H-9), 3.99-3.38 (m, 3H, CH_2CH), 3.68 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3); IR (KBr): 1744, 1729, 1718 cm^{-1}. Anal. Calcd for $C_{22}H_{15}F_6NO_4$: C, 56.06; H, 3.21; N, 2.97. Found: C, 56.03; H, 3.26; N, 2.95.

Methyl 4-hydroxy-2-methyl-1-(prop-2-ynyl)-6-(2,2,2-trifluoroacetyl)-4-trifluoromethyl-1,4-dihydrobenzo[*h*]quinoline-3-carboxylate (11): mp 173-174 °C (*n*-C_6H_{14}/EtOAc); ^{1}H NMR ($CDCl_3$): δ 8.87-8.64 (m, 1H, H-7), 8.46-8.14 (m, 2H, H-5, H-10), 7.95-7.66 (m, 2H, H-8, H-9), 5.96 (s, 1H, OH), 4.55 (dq_{AB}, *J* = 2.5, 17.0 Hz, Δδ = 1.05 ppm, 2H, CH_2), 3.60 (s, 3H, OCH_3), 2.10 (t, *J* = 2.5 Hz, 1H, C≡CH), 1.76 (s, 3H, CH_3); IR (KBr): 3275, 3235, 2104, 1745, 1709 cm^{-1}. Anal. Calcd for $C_{22}H_{15}F_6NO_4$: C, 56.06; H, 3.21; N, 2.97. Found: C, 55.81; H, 3.56; N, 2.77.

2-Oxo-1-(prop-2-ynyl)-6-(2,2,2-trifluoroacetyl)-4-trifluoromethyl-1,2-dihydrobenzo[*h*]quinoline-3-carbonitrile (12): mp 235 °C (dec.) (CH_2Cl_2/$CHCl_3$); ^{1}H NMR (CD_3CN/$CDCl_3$): δ 9.20-8.80 (m, 2H, H-7, H-10), 8.58 (br s, 1H, H-5), 8.07-7.84 (m, 2H, H-8, H-9), 4.98 (d, *J* = 2.5 Hz, 2H, CH_2), 2.90 (t, *J* = 2.5 Hz, 1H, C≡CH); IR (KBr): 3284, 2216, 2112, 1727, 1713 cm^{-1}. Anal. Calcd for $C_{20}H_8F_6N_2O_2$: C, 56.89; H, 1.91; N, 6.63. Found: C, 57.05; H, 1.94; N, 6.44.

2-Amino-4-hydroxy-1-(prop-2-ynyl)-6-(2,2,2-trifluoroacetyl)-4-trifluoromethyl-1,4-dihydrobenzo-[*h*]quinoline-3-carbonitrile (13): mp 215 °C (dec.) (CH_2Cl_2/$CHCl_3$); ^{1}H NMR (CD_3CN/$CDCl_3$): δ 9.02-8.85 (m, 1H, H-7), 8.60-8.34 (m, 2H, H-5, H-10), 7.96-7.71 (m, 2H, H-8, H-9), 5.72 (br s, 2H, NH_2),

5.06 (s, 1H, OH), 4.52 (d, J = 2.5 Hz, 2H, CH_2), 2.87 (t, J = 2.5 Hz, 1H, C≡CH); IR (KBr): 3500, 3410, 3300, 3244, 2188, 2112, 1687 cm^{-1}. Anal. Calcd for $C_{20}H_{11}F_6N_3O_2$: C, 54.68; H, 2.52; N, 9.57. Found: C, 54.75; H, 2.52; N, 9.50.

Hydrolysis of 13 into 12

To a solution of **13** (1.32 g, 3 mmol) in THF (24 mL) was added 6N HCl (6 mL) and the solution was stirred at room temperature for 4 h. The mixture was extracted with CH_2Cl_2 (50 mL), washed with sat. aq. Na_2CO_3 (100 mL), and dried over Na_2SO_4. Evaporation of the solvent gave the practically pure **12** (1.19 g, 2.82 mmol, 94%).

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