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

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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 1H-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,\(^2a,e,d\) antitumor drugs\(^2b,e,f\), and antimalarial activity.\(^4c\) They are also known to be applicable to potent and selective \(\alpha\)-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).\(^2\)

![Scheme 1](image-url)
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 1H-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. 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 CF₃-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

![Figure 1](image-url)
Table 1  Reaction of N-Propargyl-2,4-bis(trifluoroacetyl)-1-naphthylamine 3 with Dialkyl Malonates

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹CH(COR²)₂ (eq)</th>
<th>Na (eq)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield a)</th>
</tr>
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<tr>
<td>1</td>
<td>H Me 3 1</td>
<td>MeOH</td>
<td>reflux (65)</td>
<td>0.5</td>
<td>5a</td>
<td>83</td>
<td></td>
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<tr>
<td>2</td>
<td>H Me 3 1</td>
<td>MeOH</td>
<td>30</td>
<td>48</td>
<td>5a / 8a</td>
<td>45 / 44</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>H Me 5 2</td>
<td>MeOH</td>
<td>0</td>
<td>72</td>
<td>7a / 8a</td>
<td>13 / 11 b)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>H Et 3 1</td>
<td>EtOH</td>
<td>reflux (78)</td>
<td>5 min</td>
<td>5b</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>H Et 3 1</td>
<td>EtOH</td>
<td>30</td>
<td>18</td>
<td>5b / 8b</td>
<td>46 / 46</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>H Et 5 2</td>
<td>EtOH</td>
<td>0</td>
<td>72</td>
<td>7b / 8b</td>
<td>42 / 51</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>H i-Pr 3 1</td>
<td>i-PrOH</td>
<td>reflux (82)</td>
<td>5 min</td>
<td>5c / 6</td>
<td>43 / 44</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>H i-Pr 3 1</td>
<td>i-PrOH</td>
<td>30</td>
<td>2</td>
<td>5c / 7c</td>
<td>35 / 53</td>
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</tr>
<tr>
<td>9</td>
<td>H i-Pr 5 2</td>
<td>i-PrOH</td>
<td>-20</td>
<td>72</td>
<td>7c</td>
<td>100</td>
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</tr>
<tr>
<td>10</td>
<td>H t-Bu 3 1</td>
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<td>30</td>
<td>18</td>
<td>5d</td>
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<tr>
<td>11</td>
<td>Me Et 3 1</td>
<td>EtOH</td>
<td>30</td>
<td>24</td>
<td>5e</td>
<td>95</td>
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</tr>
</tbody>
</table>

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

reactive di-t-butyl malonate and diethyl methymalonate, 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-1H-benzo[h]quinolin-2-one (7a) and its dehydrated product, 1H-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-1H-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).

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 1H-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
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
acetylacetone (entry 1), to give the corresponding benzoylethylbenzo[h]quinoline (9b) (entry 3). Besides, in the reaction with unsymmetrical β-diketones, benzoylectone, 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.

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 1H-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 (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$_2$SO$_4$. 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$_2$SO$_4$. 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 malononitrile,
quenched with sat. NH₄Cl instead of 1N HCl.

**Dimethyl 2-(6-(2,2,2-trifluoroacetyl)-4-trifluoromethylbenzo[h]quinolin-3-ylmethyl)malonate (5a):**

mp 117-118 °C (n-C₆H₁₄/CHCl₃); ¹H NMR (CDCl₃): 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, CH₂CH), 3.74 (s, 6H, OCH₃); IR (KBr): 1751, 1738, 1710 cm⁻¹. Anal. Calcd for C₂₂H₁₅F₆NO₅: 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-C₆H₁₄/CHCl₃); ¹H NMR (CDCl₃): 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, CH₂CH₃), 3.80-3.65 (m, 3H, CH₂CH), 1.21 (t, J = 7.0 Hz, 6H, CH₂CH₃); ¹³C NMR (CDCl₃): δ 182.1 (q, JₐCF = 34.2 Hz), 168.3, 156.5, 148.0, 133.2 (q, JₐCF = 29.3 Hz), 131.5, 130.7, 130.4, 128.9, 128.5, 128.2, 127.6, 125.3, 124.9, 124.6 (q, JₐCF = 277.9 Hz), 119.2, 116.7 (q, JₐCF = 293.0 Hz), 62.2, 53.5, 31.1, 14.1; IR (KBr): 1733, 1718, 1710 cm⁻¹. Anal. Calcd for C₂₄H₁₉F₆NO₅: 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-C₆H₁₄/CHCl₃); ¹H NMR (CDCl₃): δ 9.22 (dd, J = 4.0, 7.0 Hz, 1H, H-2), 8.99 (s, 1H, H-5), 8.56 (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, CH₂CH), 1.25 (t, J = 6.0 Hz, 6H, CH₃), 1.17 (d, J = 6.0 Hz, 6H, CH₃); IR (KBr): 1749, 1727, 1714 cm⁻¹. Anal. Calcd for C₂₆H₂₃F₆NO₅: 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-C₆H₁₄); ¹H NMR (CDCl₃): 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), 7.88-7.55 (m, 2H, H-8, H-9), 3.76-3.47 (m, 3H, CH₂CH), 1.41 (s, 18H, CH₃); IR (KBr): 1737, 1716, 1706 cm⁻¹. Anal. Calcd for C₂₈H₃₇F₆NO₅: C, 58.86; 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-C₆H₁₄/EtOAc); ¹H NMR (CDCl₃): 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, CH₂CH₃), 3.79 (q, JₐHF = 2.0 Hz, 2H, CH₂), 1.41 (s, 3H, CH₃), 1.24 (t,
Diisopropyl 2-((2,2,2-trifluoro-1-hydroxyethyl)-4-trifluoromethylbenzo[h]quinolin-3-ylmethyl)-malonate (6): mp 107-108 °C (n-C₆H₁₄/EtOAc); ¹H NMR (CDCl₃): 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, J₉HF = 7.0 Hz, 1H, CHCF₃), 5.03 (hp, J = 6.0 Hz, 2H, OCH), 4.33-3.21 (br, 1H, OH), 3.72-3.49 (m, 3H, CH₂CH₃), 1.23 (d, J = 6.0 Hz, 6H, CH₃), 1.15 (d, J = 6.0 Hz, 6H, CH₃); IR (KBr): 3420, 1745, 1723 cm⁻¹. Anal. Calcd for C₂₆H₂₅F₆NO₅: 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-C₆H₁₄); ¹H NMR (CDCl₃): 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, CH₂), 4.17 (s, 1H, CH), 3.65 (s, 3H, OCH₃), 2.44 (t, J = 2.5 Hz, 1H, C≡CH); IR (KBr): 3330, 3270, 2120, 1741, 1734, 1685 cm⁻¹. Anal. Calcd for C₂₁H₁₃F₆NO₅: 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-C₆H₁₄); ¹H NMR (CDCl₃): 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, CH₂), 4.21 (s, 1H, CH), 4.15 (q, J = 7.0 Hz, 2H, CH₂CH₃), 2.52 (t, J = 2.5 Hz, 1H, C≡CH), 1.05 (t, J = 7.0 Hz, 3H, CH₂CH₃); IR (KBr): 3320, 3260, 2116, 1743, 1734, 1683 cm⁻¹. Anal. Calcd for C₂₂H₁₅F₆NO₅: 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 (CHCl₃); ¹H NMR (CDCl₃): 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, CH₂), 4.13 (s, 1H, CH), 2.50 (t, J = 2.5 Hz, 1H, C≡CH), 1.18 (d, J = 6.0 Hz, 3H, CH₃), 0.82 (d, J = 6.0 Hz, 3H, CH₃); IR (KBr): 3345, 3288, 2133, 1746, 1708, 1688 cm⁻¹. Anal. Calcd for C₂₃H₁₇F₆NO₅: 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_{6}H_{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_{6}NO_{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_{6}H_{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, CH_{2}CH_{3}), 2.72 (t, J = 2.5 Hz, 1H, C≡CH), 1.41 (t, J = 7.0 Hz, 3H, CH_{2}CH_{3}); IR (KBr): 3290, 2108, 1745, 1738, 1696 cm^{-1}. Anal. Calcd for C_{22}H_{13}F_{6}NO_{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_{6}H_{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_{6}NO_{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_{2}Cl_{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_{2}Cl_{2} (50 mL), washed with sat. Na_{2}CO_{3} (100 mL), with 1N HCl (100 mL), and dried over Na_{2}SO_{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_{6}H_{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_{2}CO), 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_{6}NO_{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-C₆H₁₄/EtOAc); ¹H NMR (CDCl₃): 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, CH₂); IR (KBr): 1706, 1680 cm⁻¹. Anal. Calcd for C₂₅H₁₅F₆NO₂: 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-C₆H₁₄); ¹H NMR (CDCl₃): 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=CH₂), 3.85-3.63 (m, 2H, CH₂); IR (KBr): 1953, 1712 cm⁻¹. Anal. Calcd for C₂₀H₁₁F₆NO: 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-C₆H₁₄/CHCl₃); ¹H NMR (CDCl₃): 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, CH₂CH), 3.68 (s, 3H, OCH₃), 2.27 (s, 3H, CH₃); IR (KBr): 1744, 1729, 1718 cm⁻¹. Anal. Calcd for C₂₂H₁₅F₆NO₄: 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)-1,4-dihydrobenzo[h]quinoline-3-carboxylate (11): mp 173-174 °C (n-C₆H₁₄/CHCl₃); ¹H NMR (CDCl₃): 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 (dqAB, J = 2.5, 17.0 Hz, Δδ = 1.05 ppm, 2H, CH₂), 3.60 (s, 3H, OCH₃), 2.10 (t, J = 2.5 Hz, 1H, C≡CH), 1.76 (s, 3H, CH₃); IR (KBr): 3275, 3235, 2104, 1745, 1709 cm⁻¹. Anal. Calcd for C₂₂H₁₅F₆NO₄: 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)-1,2-dihydrobenzo[h]quinoline-3-carbonitrile (12): mp 235 °C (dec.) (CH₂Cl₂/CHCl₃); ¹H NMR (CD₂CN/CDCl₃): 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, CH₂), 2.90 (t, J = 2.5 Hz, 1H, C≡CH); IR (KBr): 3284, 2216, 2112, 1727, 1713 cm⁻¹. Anal. Calcd for C₂₀H₈F₆N₂O₂: 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.) (CH₂Cl₂/CHCl₃); ¹H NMR (CD₂CN/CDCl₃): 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, NH₂),
5.06 (s, 1H, OH), 4.52 (d, J = 2.5 Hz, 2H, CH₂), 2.87 (t, J = 2.5 Hz, 1H, C≡CH); IR (KBr): 3500, 3410, 3300, 3244, 2188, 2112, 1687 cm⁻¹. Anal. Calcd for C₂₀H₁₁F₆N₃O₂: 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 CH₂Cl₂ (50 mL), washed with sat. aq. Na₂CO₃ (100 mL), and dried over Na₂SO₄. Evaporation of the solvent gave the practically pure **12** (1.19 g, 2.82 mmol, 94%).

**REFERENCES**

6. (a) M. Hojo, R. Masuda, E. Okada, and H. Miya, *Synthesis*, 1989, **550**; (b) M. Hojo, R. Masuda, and
