A Novel Procedure for the Synthesis of Benzo[b][1,8]naphthyridine-3-carboxylate Derivatives from Morita–Baylis–Hillman Adduct Acetates

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Abstract: A novel procedure has been designed for the preparation of benzo[b][1,8]naphthyridine-3-carboxylate derivatives from the reaction of Morita–Baylis–Hillman adduct acetates with primary amines, ammonium acetate or benzenesulfonamides. The approach, which involves readily available starting materials and mild reaction conditions, gives excellent yields after a convenient workup procedure.

Key words: benzo[b][1,8]naphthyridine, Morita–Baylis–Hillman adduct acetates, primary amines, ammonium acetate, benzenesulfonamides

Quinoline and its annelated derivatives1 are well known to both synthetic and biological chemists. They are important structural units present in many biologically important molecules that show a broad range of biological activities.2,3

To our knowledge, only one preparative method has been reported in the literature (Scheme 1).3 This approach uses methyl 3-(2-chloroquinolin-3-yl)acrylate as substrate in combination with methylamine in acetonitrile and is followed by reaction with the Vilsmeier reagent. The method finally afforded methyl benzo[b][1,8]naphthyridine-3-carboxylate (1) in only 42% yield. However, this approach has several drawbacks, including harsh reaction conditions, low reaction efficiency, and requires the use of hazardous and toxic reagents. In addition, the preparation of 1,2-dihydrobenzo[b][1,8]naphthyridines has not so far been documented. Thus, the development of simple and efficient methods for selectively constructing such heterocycles employing ‘green’ reaction conditions remains highly desirable.

The Morita–Baylis–Hillman (MBH) reaction is a well known coupling reaction of aldehydes and activated alkenes, which takes place in the presence of a tertiary base and affords a highly functionalized product. The versatility of the reaction has led to an exponential increase in the synthetic utility of this approach over the last decade,4 and increasing numbers of research groups have initiated work on different facets of this reaction.5,6

To access structurally complex and diverse molecules through simple starting substrates under mild reaction conditions has been one of the underlying principles of chemical research.7 During our ongoing studies toward the exploitation of MBH adduct acetates in heterocyclic chemistry, we have reported that several oxygen- and nitrogen-fused heterocycles, including polyhydrochromenes, polyhydroquinolines and 1,2,4-triazole derivatives, could be readily synthesized from MBH adducts under solvent-free conditions with good to excellent yields.8 Moreover, very recently, the direct conversion of acetanilides into 2-chloro-3-formyl quinolines 2 in good isolated yields, has been successfully achieved.9 It occurred to us that it would be useful to directly convert MBH adduct acetates such as 3 (derived from 2-chloro-3-formyl quinolines) into the desired title compounds by treatment under environmentally benign and clean conditions.

Herein, we wish to report a simple methodology for constructing the target compounds under environmentally friendly conditions.

Scheme 1

At the onset of the research, we examined the MBH reaction between 2-chloro-3-formyl quinolines 2 and activated alkenes at room temperature, in the presence of DABCO as a base, under solvent-free conditions. The MBH adducts were then transformed into the acetates 3 via acetylation with acetyl chloride (Scheme 2). The results, illustrated in Table 1, show that the substituent group played a minimal role in governing the reactivity of the substrates.

Generally, the MBH reaction proceeded well and afforded the desired products 3a–f in moderate overall yields (Table 1).
In light of the successful formation of the MBH adduct acetates 3, we intended to test the one-pot construction of methyl benzo[b][1,8]naphthyridine-3-carboxylate (1), from the MBH adduct acetate 3a and tosylamide (Scheme 3). The reaction conditions were optimized and the results are summarized in Table 2. When an equimolar amount of substrate 3a was mixed with tosylamide and 1.1 equivalents of potassium carbonate in N,N-dimethylformamide at 120 °C for five hours, the target compound 1 was successfully synthesized in 80% isolated yield. Interestingly, when an excess of tosylamide (2.5 equiv) was used under the same conditions, the unexpected product 5a was exclusively obtained in 85% yield (Scheme 4).

We presumed that the formation of product 5a might proceed through a two-step successive reaction: S_N2 substitution cyclization of the tosylamide with the MBH adduct acetate 3a, followed by a 1,4-addition process. Enlightened by the research and in order to confirm our hypothesis, the reaction was carried out as shown in Scheme 5. Cyclization of compound 3a with tosylamide (1.0 equiv) yielded the intermediate compound 4p, which was then treated with p-chlorobenzenesulfonamide (1.5 equiv) and stirred for four hours. The progress of the reaction was monitored by TLC. Gratifyingly, the desired product 5b was successfully isolated in good yield (83%).

Encouraged by these results, we further investigated the formation of 1,2-dihydrobenzo[b][1,8]naphthyridine-3-carboxylates 4 from MBH adduct acetates 3 and either primary amines or ammonium acetate. Preliminary experiments were carried out using compound 3a and aniline (Scheme 6) as typical substrates. The reaction was performed in acetone at room temperature for 10 hours without any catalyst or additive. Unfortunately, the desired product 4a was obtained in only 45% yield (Table 3, entry 1). In order to optimize the reaction conditions, various factors including bases, solvents, reaction temperature and time were investigated and the results are summarized in Table 3. In the presence of either

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base (1.1 equiv)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>K_2CO_3</td>
<td>120</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>Et_3N</td>
<td>120</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>95% EtOH</td>
<td>K_2CO_3</td>
<td>reflux</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>95% EtOH</td>
<td>Et_3N</td>
<td>reflux</td>
<td>30</td>
<td>20</td>
</tr>
</tbody>
</table>

^a Reaction conditions: 3a (1 equiv), TsNH_2 (1 equiv), K_2CO_3 (1.1 equiv), DMF, 120 °C, 5 h.
^b Isolated yield based on 3a.

Interestingly, when an excess of tosylamide (2.5 equiv) was used under the same conditions, the unexpected product 5a was exclusively obtained in 85% yield (Scheme 4).

We presumed that the formation of product 5a might proceed through a two-step successive reaction: S_N2 substitution cyclization of the tosylamide with the MBH adduct acetate 3a, followed by a 1,4-addition process. Enlightened by the research and in order to confirm our hypothesis, the reaction was carried out as shown in Scheme 5. Cyclization of compound 3a with tosylamide (1.0 equiv) yielded the intermediate compound 4p, which was then treated with p-chlorobenzenesulfonamide (1.5 equiv) and stirred for four hours. The progress of the reaction was monitored by TLC. Gratifyingly, the desired product 5b was successfully isolated in good yield (83%).

Encouraged by these results, we further investigated the formation of 1,2-dihydrobenzo[b][1,8]naphthyridine-3-carboxylates 4 from MBH adduct acetates 3 and either primary amines or ammonium acetate. Preliminary experiments were carried out using compound 3a and aniline (Scheme 6) as typical substrates. The reaction was performed in acetone at room temperature for 10 hours without any catalyst or additive. Unfortunately, the desired product 4a was obtained in only 45% yield.
triethylamine or potassium carbonate, the required reaction time could be significantly reduced and higher yields were observed (Table 3, entries 3 and 5). When the reaction was carried out at elevated temperature, compound 4a was formed in good yield within a shorter reaction time, however, the formation of some unknown byproducts were also observed (Table 3, entry 7). After screening a variety of reaction media, 95% ethanol was determined to be the best solvent for generation of the desired product (Table 3, entries 4 and 5). It is worthwhile mentioning that the workup procedure was very convenient; the product could be isolated by simple filtration without further purification when this reaction was performed at room temperature using 95% ethanol as a solvent and triethylamine as a base.

With the optimal conditions established, a series of primary amines, ammonium acetate and tosylamide were reacted with MBH adduct acetates in order to assess the scope of this method (Table 4).

As shown in Table 4, the reaction was compatible with a variety of primary amines. It can be seen that the primary amines with electron-withdrawing groups required longer reaction times and gave lower yields than those of primary amines with electron-donating groups. The presence of electron-withdrawing or electron-donating groups in substrate 3 did not appear to exert much influence on either the rate or efficiency of the reaction (Table 4, entries 5 and 6). On the other hand, the presence of a nitrile in substrate 3 gave a lower yield than those of the esters (Table 4, entry 4).

According to the above results, a possible mechanism for the formation of compounds 1, 4 and 5 from MBH adduct acetates 3 can be illustrated as shown in Scheme 7.

In summary, we have developed a novel and efficient strategy for the synthesis of various target compounds from MBH adducts and either primary amines, ammonium acetate or benzenesulfonamides under environmentally friendly and clean conditions. The merits of the present process are the simple experimental procedure, high selectivity and high to excellent yields.

Melting points were determined using a Büchi B-540 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet Avatar-370 instrument. 1H and 13C NMR spectra were recorded on Varian (400 MHz) instruments using TMS as an internal standard.

Table 3  Synthesis of Methyl 1-Phenyl-1,2-dihydrobenzo[b][1,8]naphthyridine-3-carboxylate (4a) under Different Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>acetone</td>
<td>–</td>
<td>r.t.</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>acetone</td>
<td>–</td>
<td>reflux</td>
<td>5</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>acetone</td>
<td>Et₃N</td>
<td>r.t.</td>
<td>5</td>
<td>75 (81)</td>
</tr>
<tr>
<td>4</td>
<td>95% EtOH</td>
<td>Et₃N</td>
<td>r.t.</td>
<td>4</td>
<td>88 (85)</td>
</tr>
<tr>
<td>5</td>
<td>95% EtOH</td>
<td>K₂CO₃</td>
<td>r.t.</td>
<td>4</td>
<td>87 (85)</td>
</tr>
<tr>
<td>6</td>
<td>EtOH</td>
<td>Et₃N</td>
<td>r.t.</td>
<td>4</td>
<td>81</td>
</tr>
<tr>
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<td>DMF</td>
<td>K₂CO₃</td>
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<td>84</td>
</tr>
<tr>
<td>8</td>
<td>DMF</td>
<td>K₂CO₃</td>
<td>r.t.</td>
<td>4</td>
<td>79</td>
</tr>
<tr>
<td>9</td>
<td>CHCl₃</td>
<td>Et₃N</td>
<td>r.t.</td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>10</td>
<td>CH₂Cl₂</td>
<td>Et₃N</td>
<td>r.t.</td>
<td>4</td>
<td>57</td>
</tr>
<tr>
<td>11</td>
<td>DMSO</td>
<td>Et₃N</td>
<td>r.t.</td>
<td>4</td>
<td>76</td>
</tr>
</tbody>
</table>

Entry conditions: 3a (1 equiv), amine (1 equiv), base (1.1 equiv).

Table 4  Synthesis of 1,2-Dihydrobenzo[b][1,8]naphthyridine-3-carboxylates 4 from MBH Adduct Acetates 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Time (h)</th>
<th>Product Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>CO₂Me</td>
<td>Ph</td>
<td>4</td>
<td>4a 88</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>CO₂Et</td>
<td>Ph</td>
<td>4</td>
<td>4b 89</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>CO₂(n-Bu)</td>
<td>Ph</td>
<td>4</td>
<td>4c 89</td>
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<tr>
<td>4</td>
<td>H</td>
<td>CN</td>
<td>Ph</td>
<td>4</td>
<td>4d 76</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>CO₂Me</td>
<td>Ph</td>
<td>4</td>
<td>4e 88</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>CO₂Me</td>
<td>Ph</td>
<td>4</td>
<td>4f 87</td>
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<tr>
<td>7</td>
<td>H</td>
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<td>4-MeC₆H₄</td>
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<tr>
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<tr>
<td>9</td>
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<td>CO₂Me</td>
<td>4-CIC₆H₄</td>
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<td>4i 84</td>
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<tr>
<td>10</td>
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<td>CO₂Me</td>
<td>3,4-F₂C₆H₄</td>
<td>5</td>
<td>4j 85</td>
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<tr>
<td>13</td>
<td>H</td>
<td>CO₂Me</td>
<td>n-Bu</td>
<td>3</td>
<td>4m 88</td>
</tr>
<tr>
<td>14</td>
<td>H</td>
<td>CO₂Me</td>
<td>t-Bu</td>
<td>3</td>
<td>4n 87</td>
</tr>
<tr>
<td>15</td>
<td>H</td>
<td>CO₂Me</td>
<td>H</td>
<td>5</td>
<td>4o 86</td>
</tr>
<tr>
<td>16</td>
<td>H</td>
<td>CO₂Me</td>
<td>Ts</td>
<td>10</td>
<td>4p 20 (89)</td>
</tr>
</tbody>
</table>

Entry conditions: 3 (1 equiv), R³NH₂ (1.1 equiv), Et₃N (1.5 equiv), r.t., 95% EtOH (5 mL).

Scheme 6

With the optimal conditions established, a series of primary amines, ammonium acetate and tosylamide were reacted with MBH adduct acetates in order to assess the scope of this method (Table 4).

As shown in Table 4, the reaction was compatible with a variety of primary amines. It can be seen that the primary amines with electron-withdrawing groups required longer reaction times and gave lower yields than those of primary amines with electron-donating groups. The presence of electron-withdrawing or electron-donating groups in substrate 3 did not appear to exert much influence on either the rate or efficiency of the reaction (Table 4, entries 5 and 6). On the other hand, the presence of a nitrile in substrate 3 gave a lower yield than those of the esters (Table 4, entry 4).

According to the above results, a possible mechanism for the formation of compounds 1, 4 and 5 from MBH adduct acetates 3 can be illustrated as shown in Scheme 7.

In summary, we have developed a novel and efficient strategy for the synthesis of various target compounds from MBH adducts and either primary amines, ammonium acetate or benzenesulfonamides under environmentally friendly and clean conditions. The merits of the present process are the simple experimental procedure, high selectivity and high to excellent yields.
an internal standard. Mass spectra were measured with a Finnigan Trace DSQ instrument. High-resolution mass spectral (HRMS) analyses were measured on an APEX (Bruker) mass III spectrometer using ESI (electrospray ionization) techniques. All spectroscopic data for the products were identical to data from authentic samples. Starting materials and solvents were purchased from common commercial sources and were used without additional purification. Silica-gel for chromatography was purchased from Qingdao Haiyang Chemical Co., Ltd. (200–300 mesh). Petroleum ether (PE), where used, had a boiling range 60–90 °C.

Synthesis of MBH Adduct Acetates (3); General Procedure

A mixture of 2-chloro-3-formyl quinoline (2; 10 mmol) and either acrylate or acrylonitrile (20 mmol) and DABCO (1.2 mmol) was added at r.t. for 2 d under solvent-free conditions. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with EtOAc (2 × 20 mL) and the combined organic layer was dried over anhydrous Na2SO4 and concentrated in vacuo. The desired product was obtained by flash column chromatography on silica gel (PE–EtOAc, 4:1) to give a white solid 2.

AcCl (9.6 mmol) at 0 °C was slowly added to a solution of 2 (10 mmol) and Et3N (9.6 mmol) in CH2Cl2 and stirred at r.t. for 30 min. After completion of the reaction, as indicated by TLC, H2O (30 mL) was added and the reaction mixture was extracted with EtOAc (2 × 20 mL). The organic phase was collected, dried over anhydrous Na2SO4 and evaporated under reduced pressure to give a crude product, which was purified by flash chromatography on silica gel (PE–EtOAc, 5:1) to give a white solid 3.

Methyl 2-[Acetoxy(2-chloroquinolin-3-yl)methyl]acrylate (3a)
White solid; mp 81.3–83.2 °C; Rf = 0.50 (hexanes–EtOAc, 4:1).
IR (KBr): 2960, 1751, 1720, 1566, 1490, 1370, 1224, 1051, 1024 cm⁻¹.

Butyl 2-[Acetoxy(2-chloroquinolin-3-yl)methyl]acrylate (3b)
Viscous oil; Rf = 0.55 (hexanes–EtOAc, 4:1).
IR (neat): 2982, 1750, 1720, 1566, 1490, 1378, 1238, 1497, 1645, 1690.

MS (ESI): m/z (%) = 334 (100) [M⁺ + 1].
HRMS: m/z [M⁺] calcd for C18H16ClNO4: 333.0768; found: 333.0762.

Ethyl 2-[Acetoxy(2-chloroquinolin-3-yl)methyl]acrylate (3c)
Viscous oil; Rf = 0.50 (hexanes–EtOAc, 4:1).
IR (neat): 2982, 1750, 1720, 1566, 1490, 1370, 1224, 1051, 1024 cm⁻¹.

MS (ESI): m/z (%) = 362 (100) [M⁺ + 1].
HRMS: m/z [M⁺] calcd for C19H18ClNO4: 361.1081; found: 361.1083.

1-(2-Chloroquinolin-3-yl)-2-cyanoallyl Acetate (3d)
White solid; mp 88.4–89.6 °C; Rf = 0.55 (hexanes–EtOAc, 4:1).
IR (KBr): 2230, 1749, 1617, 1399, 1208, 1035 cm⁻¹.
Methyl 2-[Acetoxy(2-chloro-6-methylquinolin-3-yl)methyl]acrylate (3e)

White solid; mp 115.7–116.6 °C; Rf = 0.50 (hexanes–EtOAc, 4:1).

IR (KBr): 3120, 1739, 1711, 1630, 1494, 1401, 1236, 1051, 821 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 2.17 (3 H, CH₃), 2.53 (3 H, CH₃), 3.74 (3 H, OCH₃), 5.80 (1 H, CH), 6.58 (1 H, CH), 7.09 (1 H, CH), 7.58 (d, J = 8.0 Hz, 1 H, ArH), 7.60 (s, 1 H, ArH), 7.92 (d, J = 8.0 Hz, 1 H, ArH), 8.04 (s, 1 H, ArH).

13C NMR (100 MHz, CDCl₃): δ = 20.8, 21.5, 52.2, 70.0, 126.6, 126.8, 127.9, 128.4, 129.6, 136.4, 145.9, 148.8, 157.0.

MS (ESI): m/z (%) = 239 (100) [M⁺ + 1].

HRMS: m/z [M⁺] calced for C₁₃H₁₁ClNO₂: 333.0771; found: 333.0771.

Preparation of Methyl Benzo[b][1,8]napthylidine-3-carboxylate (4b); General Procedure

To a solution of MBH adduct acetate 3 (1 mmol) in 95% EtOH (5 mL), was added either ammonium acetate (1.1 mmol) or primary amine (1.1 mmol) and Et₃N (1.5 mmol). The mixture was stirred vigorously at rt. for 4 h, and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction was cooled to 0 °C and the desired product 4 was obtained by simple filtration without further purification.
1-Phenyl-1,2-dihydrobenzo[b][1,8]naphthyridine-3-carboxylate (4d)

Yellow solid; mp 179.8–182.1 °C; Rf = 0.60 (hexanes–EtOAc, 4:1).

IR (KBr): 3143, 2201, 1641, 1619, 1493, 1400, 753 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 4.81 (s, 2 H, CH₂), 7.20–7.29 (m, 3 H, ArH), 7.37–7.47 (m, 6 H, ArH), 7.55 (d, J = 8.0 Hz, 1 H, ArH), 7.64 (s, 1 H, ArH).

13C NMR (100 MHz, CDCl₃): δ = 38.9 (CH₂), 125.9, 127.2, 127.8, 129.0 (2 CH), 131.0, 136.3, 138.6, 143.2, 148.6, 152.5.

MS (ESI): m/z (%) = 350 (100) [M + 1].


Methyl 7-Methyl-1-phenyl-1,2-dihydrobenzo[b][1,8]naphthyridine-3-carboxylate (4e)

Yellow solid; mp 210.0–211.7 °C; Rf = 0.60 (hexanes–EtOAc, 4:1).

1H NMR (400 MHz, CDCl₃): δ = 2.40 (s, 3 H, CH₃), 3.83 (s, 3 H, OCH₃), 4.87 (s, 2 H, CH₂), 7.25–7.32 (m, 3 H, ArH), 7.44–7.52 (m, 5 H, ArH), 7.59–7.66 (m, 3 H, ArH), 8.06 (s, 1 H, ArH).

13C NMR (100 MHz, CDCl₃): δ = 131.0, 133.8, 136.2, 137.0, 148.8, 153.8, 157.3, 165.1.

MS (ESI): m/z (%) = 347 (100) [M⁺ + 1].


Methyl 1-(4-Chlorophenyl)-1,2-dihydrobenzo[b][1,8]naphthyridine-3-carboxylate (4j)

Yellow solid; mp 208.5–209.9 °C; Rf = 0.60 (hexanes–EtOAc, 4:1).

IR (KBr): 3139, 3007, 1715, 1651, 1613, 1509, 1443, 1381, 1239, 1180 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 3.81 (s, 3 H, OCH₃), 3.85 (s, 3 H, OCH₃), 4.86 (s, 2 H, CH₂), 6.96–6.99 (m, 2 H, ArH), 7.13 (t, J = 8.0 Hz, 1 H, ArH), 7.32–7.44 (m, 4 H, ArH), 7.49 (d, J = 8.0 Hz, 2 H, ArH), 7.60 (s, 1 H, ArH).

13C NMR (100 MHz, CDCl₃): δ = 117.7, 122.9, 124.2, 125.2, 126.9, 127.0 (2 CH), 127.6, 130.3, 133.8, 136.2, 137.0, 148.8, 153.7, 157.3, 165.1.

MS (ESI): m/z (%) = 353 (100) [M⁺ + 1].

HRMS: m/z [M⁺] calcd for C₂₃H₂₄N₂O₂: 358.1683; found: 358.1691.

Methyl 1-(4-Methoxyphenyl)-1,2-dihydrobenzo[b][1,8]naphthyridine-3-carboxylate (4h)

Yellow solid; mp 208.5–209.9 °C; Rf = 0.60 (hexanes–EtOAc, 4:1).

IR (KBr): 3139, 3007, 1715, 1651, 1613, 1509, 1443, 1381, 1239, 1180 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 3.81 (s, 3 H, OCH₃), 3.85 (s, 3 H, OCH₃), 4.86 (s, 2 H, CH₂), 6.96–6.99 (m, 2 H, ArH), 7.13 (t, J = 8.0 Hz, 1 H, ArH), 7.32–7.44 (m, 4 H, ArH), 7.49 (d, J = 8.0 Hz, 2 H, ArH), 7.60 (s, 1 H, ArH).

13C NMR (100 MHz, CDCl₃): δ = 35.0, 50.4, 52.0, 116.8, 122.4, 123.8, 124.7, 126.3, 127.2, 127.7, 128.4 (2 CH), 128.5 (2 CH), 130.4, 133.8, 136.1, 137.4, 149.4, 153.7, 165.2.

MS (ESI): m/z (%) = 331 (100) [M⁺ + 1].

HRMS: m/z [M⁺] calcd for C₂₃H₂₄N₂O₂: 358.1683; found: 358.1691.
HRMS: m/z [M⁺] calcd for C_{21}H_{18}N_2O_4S: 394.0987; found: 394.0986.

Methyl 1-Tert-Butyl-1,2-dihydrobenzo[1,8]naphthyridine-3-carboxylate (5b)
A stirred solution of 3a (319 mg, 1 mmol), TsNH₂ (430 mg, 2.5 mmol), and K₂CO₃ (152 mg, 1.1 mmol) in DMF (5 mL) was heated at 90 °C for 15 min. After completion of the reaction, as indicated by TLC, H₂O (10 mL) was added and the reaction mixture was extracted with EtOAc (3 × 10 mL). The organic phase was collected, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure to give the crude product 5b, which was purified by flash chromatography on silica gel (PE–EtOAc: 2:1).

Yield: 346 mg (85%); yellow solid; mp 271.5–273.4 °C; R_f = 0.30 (hexanes–EtOAc, 2:1).

IR (KBr): 1725, 1644, 1608, 1595, 1524, 1480, 1452, 1413, 1388, 1351, 1290, 1244, 1213, 1189, 1149, 1120, 1088, 1056, 1016, 990, 942, 923, 894, 802, 722, 691, 643, 606 cm⁻¹.

HRMS: m/z [M⁺] calcd for C_{21}H_{18}N_2O_4S: 394.0987; found: 394.0986.

Methyl 4-(4-Methylphenylsulfonylamo)benzo[b][1,8]naphthyridine-3-carboxylate (5a)

yield: 346 mg (85%); yellow solid; mp 271.5–273.4 °C; R_f = 0.30 (hexanes–EtOAc, 2:1).

IR (KBr): 1725, 1644, 1608, 1595, 1524, 1480, 1452, 1413, 1388, 1351, 1290, 1244, 1213, 1189, 1149, 1120, 1088, 1056, 1016, 990, 942, 923, 894, 802, 722, 691, 643, 606 cm⁻¹.

HRMS: m/z [M⁺] calcd for C_{21}H_{18}N_2O_4S: 394.0987; found: 394.0986.

Methyl 1,2-Dihydrobenzo[b][1,8]naphthyridine-3-carboxylate (4d)
A stirred solution of 3a (319 mg, 1 mmol), TsNH₂ (172 mg, 1 mmol), and K₂CO₃ (152 mg, 1.1 mmol) in DMF (5 mL) was heated at 90 °C for 15 min. p-Chlorobenzensulfonylamine (287 mg, 1.5 mmol) was added and the reaction was stirred at 120 °C for 4 h. After completion of the reaction, as indicated by TLC, H₂O (10 mL) was added and the reaction mixture was extracted with EtOAc (3 × 10 mL). The organic phase was collected, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure to give the crude product 5b, which was purified by flash chromatography on silica gel (PE–EtOAc: 2:1).

Yield: 354 mg (83%); yellow solid; mp 272.0–273.6 °C; R_f = 0.30 (hexanes–EtOAc, 2:1).

IR (KBr): 3427, 3170, 1724, 1619, 1508, 1400, 1259, 1080 cm⁻¹.
1H NMR (400 MHz, CDCl3): δ = 4.01 (s, 3 H, OCH3), 7.40 (t, J = 8.0 Hz, 1 H, ArH), 7.52–7.57 (m, 3 H, ArH), 7.77 (t, J = 8.0 Hz, 1 H, ArH), 8.05–8.09 (m, 2 H, ArH), 8.68 (d, J = 8.0 Hz, 1 H, ArH), 9.27 (s, 1 H, ArH), 9.84 (s, 1 H, ArH).

13C NMR (100 MHz, CDCl3): δ = 52.6, 112.2, 117.4, 119.9, 120.5, 124.0, 127.7 (2 × CH), 128.9 (2 × CH), 129.1, 135.2, 137.9, 139.7, 141.8, 142.6, 151.0, 155.8, 161.2, 165.0.

MS (ESI): m/z (%) = 426 (100) [M+ – 1].

HRMS: m/z [M+] calcd for C20H14ClN3O4S: 427.0394; found: 426.4 (100) [M+ – 1].

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References


