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*Research Letter*

# Three-Component One-Pot Synthesis of Novel Benzo[*b*]1,8-naphthyridines Catalyzed by Bismuth(III) Chloride

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A novel and efficient three-component one-pot synthesis of benzo[*b*]1,8-naphthyridines by 2-amino-4-methylquinoline, aromatic aldehydes, and malononitrile was done. The reaction was catalyzed by an acidic Bismuth(III) chloride, functionalized Bismuth(III) chloride, at room temperature to give various benzo[*b*]1,8-naphthyridines in high yields. The Bismuth(III) chloride is an environmentally friendly catalyst.



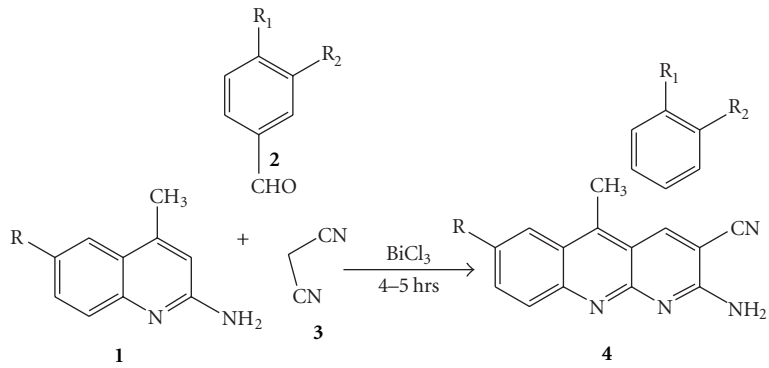
## 1. Introduction

One of the most important reactions in organic chemistry for the formation of carbon—carbon bonds—is the multicomponent reactions (MCRs) and much effort has been devoted to the development of this reactions in recent years [1, 2].

Among the nitrogen heterocycles, naphthyridines and their derivatives represent an important class of organic molecules that attract the interest of both synthetic and medicinal chemists. Functionalized naphthyridines have found applications as pharmaceuticals, fungicides, bactericides, herbicides, and insecticides as well as useful synthetic blocks in the preparation of several alkaloids [3–6]. Many syntheses of naphthyridines are known, but due to their importance, the development of new synthetic approaches remains an active research area [7, 8].

Various procedures are available for the synthesis of benzo[*b*]1,8-naphthyridines. However, there are several disadvantages associated with these methodologies including unsatisfactory yields, long conversion times and inflammable organic solvents. In recent years, we have initiated our efforts on the development of simple methods for the synthesis of naphthyridines derivatives [9–11]. Hence, now we report herein a useful, general approach towards the formation of benzo[*b*]1,8-naphthyridines in one-pot operation (Scheme 1). This method permits the condensation of aromatic 2-amino-4-methylquinoline 1, aldehyde 2, and malononitrile 3using Lewis acid catalysts under mild conditions to afford diverse benzo[*b*]1,8-naphthyridines (4a–h) and is also amenable to small library production using solid-phase techniques.

In addition, there has been an intense interest in the selection of different catalysts in development of new methods for MCRs. The utility of different metal salts such as mercuric salts, lead salts, zinc chloride, cadmium chloride, and indium chloride, lanthanide compounds, $InBr_3$, $ZrCl_4$ [12, 13], as potential catalyst in variety of synthetic reactions was recognized in recent years. However, the expensiveness and toxicity of some metal salts hampers their wide applications in organic synthesis. On the other hand, in recent years, economically affordable ecofriendly catalysts received some interest in various organic reactions. The application of some of these catalysts such as Cu(II) salts [14], Fe(II)/Fe(III) salts [15], nickel salts, and Bismuth(III) salts [16, 17] as catalysts in organic synthesis, has been investigated extensively. Bismuth trichloride has received considerable attention as an inexpensive, nontoxic, and readily available catalyst for various organic transformations,




Scheme 1: The synthesis of benzo[*b*]1,8-naphthyridines.

affording the corresponding products in excellent yields with high selectivity (Scheme 1).

Equimolar of various substituted aromatic aldehyde 2 reacted well with 2-amino-4-methylquinoline 1 and malononitrile 3 in presence of 10 mol% of $BiCl_3$ catalyst in $CH_3CN$ solvent to give the corresponding substituted naphthyridine 4a-h in 93–97% yields. In each experiment, molar ratio 1:1:1.5 of the three components 1, 2, and 3 were used as reactants. The method is very simple and it can be used as derivatives of substituted 2-amino-4-methylquinoline 1, different substituted aromatic aldehyde 2, and malononitrile 3 to prepare different substituted naphthyridine derivatives (Table 1).

## 2. Experimental

Melting points were recorded on an open capillary tube with a Buchi melting point apparatus and are uncorrected. Elemental analyses were carried out using Perkin-Elmer 24°C CHN-analyzer. IR spectra were recorded on an FT-IR infrared spectrophotometer. $^1$H-NMR spectra were obtained using a 300 MHz on a Bruker spectrometer (chemical shifts in $\delta$ ppm). Mass spectra were recorded on an LC MS Mass spectrometer.

### 2.1. General Procedure

A mixture of 2-amino-4-methylquinoline (1 mmol), aromatic aldehyde (1.5 mmol), and malononitriles (1 mmol) in anhydrous $CH_3CN$ (15 mL) was stirred at room temp for 30 minutes. $BiCl_3$ (20 mol%) was added over a period of 20 minutes. The resulting mixture was stirred for 4-5 hours. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 15 mL). The organic layer was separated, dried ($Na_2SO_4$), and concentrated, and the resulting product was recrystalized to afford pure benzo[*b*]1,8-naphthyridines 4a. The same procedure was used for the synthesis of 4b–h. The physicochemical data for the synthesized compounds are as shown below.

**4a:** M.p. 160–163°C. IR (KBr): 3251; 1723; cm$^{-1}$. $^1$H NMR (DMSO $d_6$): 1.20 (s, 3H, $CH_3$), 6.33 (s, 2H, $NH_2$), 6.80–7.40 (m, 5Harom), 7.45 (d, 1H, $J$ = 8.5), 7.51 (d, 1H, $J$ = 8.5), 7.70–7.72 (m, 2Harom), 21.5, 89.2, 118.5 (CN), 121.4, 124.5, 126.7, 127.5, 127.6, 127.7, 129.4, 129.5, 129.6, 129.5, 129.4, 138.3, 138.8, 146.8, 152.6, 160.6, 162.5 ($NH_2$), mass m/z:310.

**4b:** M.p. 162–165°C. IR (KBr): 3251; 1723; cm$^{-1}$. $^1$H NMR (DMSO $d_6$): 1.26 (s, 3H, $CH_3$), 1.80 (s, 3H, $CH_3$), 6.30 (s, 2H, $NH_2$), 6. 68–7.25 (m, 5Harom), 7.36 (d, 1H, $J$ = 8.5), 7.42–7.45 (m, 3Harom), 21.3, 24. 9, 89.0, 118.4 (CN), 121.3, 124.2, 126.8, 127.3, 127.6, 127.4, 129.2, 129.5, 129.3, 129.4, 129.7, 138.0, 138.7, 146.7, 152.4, 160.3, 162.4 ($NH_2$), mass m/z:324.

**4c:** M.p. 171–173°C. IR (KBr): 3251; 1723; cm$^{-1}$. $^1$H NMR (DMSO $d_6$): 1.22 (s, 3H, $CH_3$), 3.10 (s, 3H, $OCH_3$), 6.25 (s, 2H, $NH_2$), 6.70–7.13 (m, 5Harom), 7.26 (d, 1H, $J$ = 8.5), 7.33–7.40 (m, 3Harom), 20.8, 25.4, 88.9, 118.3 (CN), 121.5, 124.5, 126.7, 127.6, 127.6, 127.8, 129.4, 129.7, 129.8, 129.8, 129.9, 138.3, 138.5, 146.8, 152.5, 160.4, 162.7 ($NH_2$), mass m/z:340.

**4d:** M.p. 178–180°C. IR (KBr): 3251; 1723; cm$^{-1}$. $^1$H NMR (DMSO $d_6$): 1.15 (s, 3H, $CH_3$), 6.20 (s, 2H, $NH_2$), 6.80–7.36 (m, 5Harom), 7.40 (d, 1H, $J$ = 8.5), 7.58–7.60 (m, 3Harom), 21.7, 89.5, 118.2 (CN), 121.3, 124.4, 126.5, 127.3, 127.6, 127.5, 129.5, 129.6, 129.5, 129.5, 129.7, 132.5(Cl), 138.5, 138.8, 146.8, 152.6, 160.5, 162.7 ($NH_2$), mass m/z:344.

**4e:** M.p. 170–173°C. IR (KBr): 3251; 1723; cm$^{-1}$. $^1$H NMR (DMSO $d_6$): 1.23 (s, 3H, $CH_3$), 1.65 (s, 3H, $CH_3$), 1.93 (s, 3H, $CH_3$), 6.20 (s, 2H, $NH_2$), 6.70–6.92 (m, 5Harom), 7.08 (d, 1H, $J$ = 8.5), 7.20–7.30 (m, 3Harom), 20.5, 23. 5, 24. 7, 89.4, 118.4 (CN), 121.5, 124.4, 126.4, 127.5, 127.6, 127.7, 129.4, 129.5, 129.6, 129.8, 129.9, 138.5, 138.6, 146.8, 152.6, 160.5, 162.9 ($NH_2$), mass m/z:338.

**4f:** M.p. 162–164°C. IR (KBr): 3251; 1723; cm$^{-1}$. $^1$H NMR (DMSO $d_6$): 1.16 (s, 3H, $CH_3$), 1.95 (s, 3H, $CH_3$), 6.20 (s, 2H, $NH_2$), 6.66–6.90 (m, 5Harom), 6.95 (d, 1H, $J$ = 8.5), 6.98–7.20 (m, 3Harom), 21.6, 25.2, 88.7, 118.0 (CN), 121.5, 124.6, 126.7, 127.5, 127.6, 127.6, 129.5, 129.6, 129.6, 129.7, 129.8, 138.5, 138.7, 146.8, 152.6, 160.5, 162.6 ($NH_2$), mass m/z:324.

Table 1: One-pot synthesis of benzo[*b*]1,8-naphthyridines.

| Entry | R | $R_1$ | $R_2$ | Product[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | H | H | H | 4a | 93 |
| 2 | $CH_3$ | H | H | 4b | 95 |
| 3 | $OCH_3$ | H | H | 4c | 95 |
| 4 | Cl | H | H | 4d | 97 |
| 5 | $CH_3$ | $CH_3$ | H | 4e | 93 |
| 6 | H | H | $CH_3$ | 4f | 95 |
| 7 | H | H | $OCH_3$ | 4g | 96 |
| 8 | H | H | Cl | 4h | 96 |

[a]All the products were characterised by IR, $^1$H NMR, and mass spectra.
[b]Yields of isolated products.

**4g:** M.p. 171–173°C. IR (KBr): 3251; 1723; $cm^{-1}$. $^1$H NMR (DMSO $d_6$): 1.21 (s, 3H, $CH_3$), 3.00 (s, 3H, $OCH_3$), 6.20 (s, 2H, $NH_2$), 6.71–7.04 (m, 5Harom), 7.10 (d, 1H, $J$ = 8.5), 7.29–7.35 (m, 3Harom), 21.2, 26.3, 89.3, 117.9 (CN), 121.5, 124.2, 126.6, 127.5, 127.5, 127.6, 129.4, 129.4, 129.5, 129.6, 129.6, 138.7, 138.9, 146.7, 152.6, 160.5, 162.7 ($NH_2$), mass m/z:340.

**4h:** M.p. 176–179°C. IR (KBr): 3251; 1723; $cm^{-1}$. $^1$H NMR (DMSO $d_6$): 1.15 (s, 3H, $CH_3$), 6.20 (s, 2H, $NH_2$), 6.75–7.20 (m, 5Harom), 7.32 (d, 1H, $J$ = 8.5), 7.35–7.38 (m, 3Harom), 21.7, 89.2, 118.3 (CN), 121.3, 124.2, 126.5, 127.3, 127.4, 127.4, 129.2, 129.3, 129.3, 129.3, 129.3, 131.5(Cl), 138.0, 138.7, 146.7, 152.4, 160.3, 162.2 ($NH_2$), mass m/z:344.

### *Elemental Analysis*

**4a**. $C_{20}H_{14}N_4$ Calc: C, 77.40; H, 4.55; N, 18.05; Found: C, 77.38; H, 4.53; N, 18.03.

**4b**. $C_{21}H_{16}N_4$ Calc: C, 77.76; H, 4.97; N, 17.27; Found: C, 77.74; H, 4.96; N, 17.24.

**4c**. $C_{21}H_{16}N_4O$ Calc: C, 74.10; H, 4.74; N, 16.46; Found: C, 74.11; H, 4.72; N, 16.43.

**4d**. $C_{20}H_{13}CIN_4$ Calc: C, 69.67; H, 3.80; N, 16.25; Found: C, 69.65; H, 3.78; N, 16.23.

**4e**. $C_{22}H_{18}N_4$ Calc: C, 78.08; H, 5.36; N, 16.56; Found: C, 78.06; H, 5.34; N, 16.53.

**4f**. $C_{21}H_{16}N_4$ Calc: C, 77.76; H, 4.97; N, 17.27; Found: C, 77.75; H, 4.95; N, 17.25.

**4g**. $C_{21}H_{16}N_4O$ Calc: C, 74.10; H, 4.74; N, 16.46; Found: C, 74.07; H, 4.73; N, 16.47.

**4h**. $C_{20}H_{13}CIN_4$ Calc: C, 69.67; H, 3.80; N, 16.25; Found: C, 69.68; H, 3.79; N, 16.24.

## 3. Conclusion

In summary, we have established a new methodology, based on a three-component reaction to obtain new substituted benzo[*b*]1,8-naphthyridines derivatives catalyzed by $BiCl_3$. The simplicity of this elegant protocol and accessibility of the starting materials allowed us to prepare these new benzo[*b*]1,8-naphthyridines derivatives that should have wide applicability in heterocyclic and medicinal chemistry.

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