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An efficient synthesis of 1-oxo-1,2-dihydrobenzo[b][1,6]naphthyridine-4-carbonitriles

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ABSTRACT

Ethyl α-(dimethylaminomethylene)-2-cyanomethyl-4-phenylquinoline-3-carboxylate (**2**) as new synthons directed to 1-oxo-1,2-dihydrobenzo[b][1,6]naphthyridine-4-carbonitriles was obtained by the condensation of ethyl 2-cyanomethyl-4-phenylquinoline-3-carboxylate (**1**) and *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA). Reaction of this enamine with primary amines (**3**) in HOAc-DMF at 120 °C then affords 2-substituted 1-oxo-1,2-dihydrobenzo[b][1,6]naphthyridine-4-carbonitrile derivatives (**4**) in good yields by a tandem addition–elimination–cyclization reaction.

1. Introduction

The [1,6]naphthyridine and their benzo-fused analogs are an important pharmacophore present in many natural [1] and designed synthetic products of therapeutic importance. They are associated with a wide spectrum of biological activities ranging from anticancer [2], anti-HIV-1 [3], antimicrobial [4] and cytotoxic activity [5]. Therefore, the synthesis of [1,6]naphthyridine derivatives has aroused great interest in organic and medicinal communities [6–10].

Earlier reports for the synthesis of benzo[b][1,6]naphthyridines has been carried out either *via* Vilsmeir–Haack reaction of 2-hydroxy-4-arylaminopyridines [11] or *via* Diels–Alder process of Mannich base of 4-hydroxy-2-quinolone with anilines [12]. Deady *et al*., have reported that synthesis of the benzo[b][1,6]naphthyridine-4-carboxylic acids by multi-step reactions of (3-carboxyquinolin-2-yl)acetate with Vilsmeier reagent [13]. Recently, Singh and coworkers reported palladium-catalyzed synthesis of benzo[b][1,6]naphthyridines *via* Sonogashira coupling and annulation reactions from 2-chloroquinoline-3-carboxaldehydes or 2-chloroquinoline-3-carbonitriles with terminal alkynes [9]. As a result, the development of simple, straightforward and efficient methods for synthesis of benzo[b][1,6]naphthyridine derivatives is strongly desirable.

In a continuation of our interest in the synthetic methodologies of fused heterocycles [14], herein we report the facile synthesis of 1-oxo-1,2-dihydrobenzo[b][1,6]naphthyridine-4-carbonitriles (**4**) by a tandem addition–elimination–cyclization reaction of ethyl α-(dimethylaminomethylene)-2-cyanomethyl-4-phenylquinoline-3-carboxylate (**2**) with primary amines (**3**) (Scheme 1).

2. Experimental

2.1. Preparation of ethyl α-(dimethylaminomethylene)-2-cyanomethyl-4-phenylquinoline-3-carboxylate (2)

To a solution of ethyl 2-cyanomethyl-4-phenylquinoline-3-carboxylate **1** [15] (6.3 g, 20.0 mmol) in DMF (20 mL) was added DMFDMA (3.8 g, 30.0 mmol) and the mixture was heated at 100 °C for 2 h. After cooling to room temperature, then water (50 mL) was added and stirred for 20 min. The solid was filtered and recrystallized from EtOH to give 6.5 g (87%) of **2**, as deep red prism. Mp 150–151 °C. IR (KBr, cm^{-1}): ν 2234 (CN), 1672 (C=O). ^1H NMR (400 MHz, $CDCl_3$): δ 1.63 (t, 3H, J = 7.2 Hz), 3.40 (s, 3H), 3.43 (s, 3H), 4.62 (q, 2H, J = 7.2 Hz), 7.20–7.25 (m, 2H), 7.43–7.50 (m, 5H), 7.89–7.90 (m, 1H), 7.85 (s, 1H), 8.32 (d, 1H, J = 10.4 Hz). Anal. Calcd. for $C_{23}H_{21}N_3O_2$: C 74.37, H 5.70, N 11.31. Found: C 74.49, H 5.86, N 11.48.

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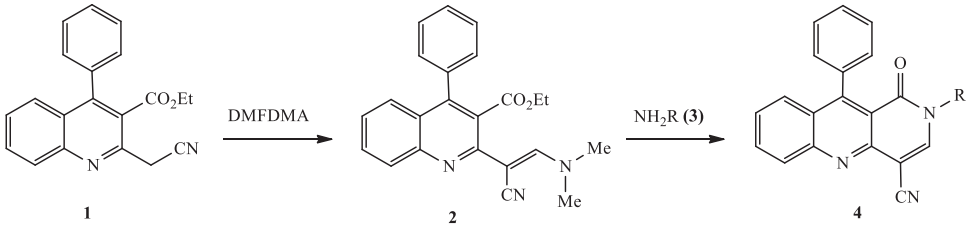

Scheme 1. Syntheses of 1-oxo-1,2-dihydrobenzo[b][1,6]naphthyridine-4-carbonitriles.

2.2. Preparation of 2-substituted 1-oxo-1,2-dihydrobenzo[b][1,6]naphthyridine-4-carbonitrile derivatives

A mixture of ethyl α-(dimethylaminomethylene)-2-cyanomethyl-4-phenyl-quinoline-3-carboxylate (**2**, 1.0 mmol), amine (**3**, 1.0 mmol) in 25 mL HOAc-DMF (1:1, v:v) was heated to reflux under stirring for 6–11 h. At the end of the reaction, cooled the mixture to room temperature, added water (20 mL) to the mixture and stirred for 30 min. The solid was filtered and recrystallized to afford the corresponding products (**4a**–**l**).

4a: Mp > 300 °C. IR (KBr, cm^{-1}): ν 2250 (CN), 1680 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.50 (s, 3H), 7.23–7.24 (m, 2H), 7.47–7.49 (m, 5H), 7.84–7.88 (m, 1H), 7.97 (s, 1H), 8.29 (d, 1H, *J* = 10.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.4, 94.1, 115.6, 116.1, 126.5, 127.1, 127.2, 127.5, 127.8, 128.6, 128.8, 129.3, 132.5, 143.7, 144.6, 149.4, 150.2, 161.5. Anal. Calcd. for $C_{20}H_{13}N_3O$: C 77.16, H 4.21, N 13.50. Found: C 77.25, H 4.37, N 13.68.

4b: Mp > 300 °C. IR (KBr, cm^{-1}): ν 2228 (CN), 1685 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, 3H, *J* = 6.4 Hz), 3.95 (q, 2H, *J* = 6.4 Hz), 7.19–7.21 (m, 2H), 7.46–7.54 (m, 5H), 7.86–7.88 (m, 1H), 7.97 (s, 1H), 8.29 (d, 1H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 44.9, 94.1, 115.8, 116.3, 126.4, 127.1, 127.2, 127.5, 127.8, 128.5, 128.7, 128.8, 129.3, 129.4, 132.4, 143.5, 149.3, 160.7. Anal. Calcd. for $C_{21}H_{15}N_3O$: C 77.52, H 4.65, N 12.91. Found: C 77.68, H 4.79, N 13.04.

4c: Mp 260–262 °C. IR (KBr, cm^{-1}): ν 2234 (CN), 1681 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, 3H, *J* = 6.4 Hz), 1.69–1.75 (m, 2H), 3.84 (q, 2H, *J* = 6.4 Hz), 7.21–7.22 (m, 2H), 7.44–7.54 (m, 5H), 7.84–7.87 (m, 1H), 7.95 (s, 1H), 8.28 (d, 1H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6, 22.5, 51.4, 94.8, 115.8, 116.3, 126.3, 127.2, 127.3, 127.4, 128.6, 128.8, 129.1, 143.2, 144.2, 145.1, 149.3, 150.2, 154.0, 160.8. Anal. Calcd. for $C_{22}H_{17}N_3O$: C 77.86, H 5.05, N 12.38. Found: C 77.97, H 5.17, N 12.49.

4d: Mp 295∼297 °C. IR (KBr, cm^{-1}): ν 2251 (CN), 1675 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, 3H, *J* = 6.4 Hz), 1.30–1.34 (m, 2H), 1.66–1.67 (m, 2H), 3.87 (q, 2H, *J* = 6.4 Hz), 7.21–7.23 (m, 2H), 7.43–7.54 (m, 5H), 7.83–7.86 (m, 1H), 7.96 (s, 1H), 8.28 (d, 1H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.3, 19.9, 31.3, 49.8, 93.8, 115.8, 116.3, 126.3, 127.1, 127.4, 128.6, 128.8, 129.1, 137.4, 143.3, 144.2, 145.2, 149.3, 150.2, 153.9, 160.8. Anal. Calcd. for $C_{23}H_{19}N_3O$: C 78.16, H 5.42, N 11.89. Found: C 78.32, H 5.58, N 11.97.

4e: Mp > 300 °C. IR (KBr, cm^{-1}): ν 2241 (CN), 1683 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17–1.24 (m, 1H), 1.33–1.52 (m, 4H), 1.70–1.73 (m, 1H), 1.87–1.89 (m, 4H), 4.75–4.82 (m, 1H), 7.21–7.24 (m, 2H), 7.44–7.46 (m, 2H), 7.54–7.56 (m, 3H), 7.84–7.85 (m, 1H), 7.80 (s, 1H), 8.28 (d, 1H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 25.6, 32.0, 32.5, 53.3, 54.7, 93.9, 116.1, 116.2, 126.3, 126.9, 127.1, 127.4, 127.5, 128.9, 132.4, 137.7, 139.9, 140.9, 141.7, 148.4, 150.2, 160.8. Anal. Calcd. for $C_{25}H_{21}N_3O$: C 79.13, H 5.58, N 11.07. Found: C 79.28, H 5.74, N 11.16.

4f: Mp > 300 °C. IR (KBr, cm^{-1}): ν 2231 (CN), 1687 (C=O). ^{1}H NMR (400 MHz, CF_3CO_2D): δ 5.22 (s, 2H), 7.24–7.28 (m, 4H), 7.36–7.37 (m, 3H), 7.61–7.66 (m, 3H), 7.87–7.88 (m, 2H), 8.32–8.37 (m, 1H), 8.56 (d, 1H, *J* = 8.4 Hz), 8.70 (s, 1H). ^{13}C NMR (100 MHz, CF_3CO_2D): δ 83.2, 111.4, 115.9, 118.9, 119.2, 125.8, 126.6, 128.2, 128.3, 128.5, 128.7, 129.1, 129.6, 133.3, 139.3, 140.2, 140.4, 144.9, 152.1, 152.4, 158.9, 168.7. Anal. Calcd. for $C_{26}H_{17}N_3O$: C 80.60, H 4.42, N 10.85. Found: C 80.73, H 4.58, N 10.95.

4g: Mp 287–289 °C. IR (KBr, cm^{-1}): ν 2242 (CN), 1676 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15–7.26 (m, 4H), 7.48–7.52 (m, 8H), 7.87–7.90 (m, 1H), 8.06 (s, 1H). 8.34 (d, 1H, *J* = 9.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 94.2, 113.2, 115.0, 116.3, 124.5, 125.6, 126.3, 128.6, 129.1, 130.1, 130.4, 130.5, 130.8, 133.7, 139.5, 140.3, 140.6, 145.3, 152.4, 159.6, 161.5. Anal. Calcd. for $C_{25}H_{15}N_3O$: C 80.41, H 4.05, N 11.25. Found: C 80.56, H 4.16, N 11.38.

4h: Mp 295–297 °C. IR (KBr, cm^{-1}): ν 2225 (CN), 1680 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (s, 3H), 7.17–7.28 (m, 6H), 7.46–7.51 (m, 5H), 7.89–7.91 (m, 1H), 7.93 (s, 1H). 8.33 (d, 1H, *J* = 9.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 94.5, 115.5, 116.6, 126.6, 126.7, 126.8, 127.0, 127.3, 127.5, 127.7, 128.6, 129.4, 130.4, 130.6, 132.6, 137.0, 143.5, 144.4, 145.6, 149.4, 150.3, 160.4. Anal. Calcd. for $C_{26}H_{17}N_3O$: C 80.60, H 4.42, N 10.85. Found: C 80.74, H 4.54, N 10.93.

4i: Mp > 300 °C. IR (KBr, cm^{-1}): ν 2257 (CN), 1673 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 7.08–7.18 (m, 2H), 7.21–7.23 (m, 3H), 7.47–7.48 (m, 5H), 7.86–7.87 (m, 1H), 8.03 (s, 1H), 8.32 (d, 1H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 94.4, 115.6, 116.6, 124.6, 126.5, 126.9, 127.1, 127.2, 127.4, 127.9, 128.7, 129.3, 130.2, 131.9, 132.6, 133.8, 143.7, 144.8, 145.6, 149.3, 150.2, 160.8. Anal. Calcd. for $C_{26}H_{17}N_3O$: C 80.60, H 4.42, N 10.85. Found: C 80.72, H 4.57, N 10.96.

4j: Mp > 300 °C. IR (KBr, cm^{-1}): ν 2242 (CN), 1670 (C=O). ^{1}H NMR (400 MHz, CF_3CO_2D): δ 2.39 (s, 3H), 7.18 (d, 2H, *J* = 8.4 Hz), 7.26–7.27 (m, 2H), 7.33 (d, 2H, *J* = 8.4 Hz), 7.58–7.60 (m, 3H), 7.91–7.96 (m, 2H), 8.38–8.39 (m, 1H), 8.63 (d, 1H, *J* = 8.8 Hz), 8.75 (s, 1H). ^{13}C NMR (100 MHz, CF_3CO_2D): δ 20.7, 113.2, 115.0, 116.0, 116.2, 124.9, 125.7, 126.5, 128.5, 129.0, 130.1, 130.3, 130.6, 130.9, 133.2, 139.4, 140.5, 140.7, 145.1, 152.9, 159.5, 169.2. Anal. Calcd. for $C_{26}H_{17}N_3O$: C 80.60, H 4.42, N 10.85. Found: C 80.75, H 4.51, N 10.98.

4k: Mp > 300 °C. IR (KBr, cm^{-1}): ν 2234 (CN), 1679 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 7.16–7.22 (m, 6H), 7.44–7.48 (m, 5H), 8.88–8.89 (m, 1H), 8.03 (s, 1H), 8.32 (d, 1H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.5, 94.4, 114.0, 115.6, 116.6, 126.5, 127.3, 127.4, 127.9, 128.6, 128.8, 129.3, 130.6, 132.6, 133.8, 143.9, 145.0. 145.8, 149.4, 150.3, 154.5, 161.0. Anal. Calcd. for $C_{26}H_{17}N_3O_2$: C 77.41, H 4.25, N 10.42. Found: C 77.53, H 4.38, N 10.57.

4l: Mp > 300 °C. IR (KBr, cm^{-1}): ν 2248 (CN), 1674 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11–7.15 (m, 2H), 7.20–7.22 (m, 2H), 7.28–7.29 (m, 2H), 7.48–7.49 (m, 5H), 7.88–7.90 (m, 1H), 8.01 (s, 1H), 8.32 (d, 1H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 95.0, 115.4, 115.9, 116.2, 116.5, 117.3, 117.5, 126.7, 127.0, 127.3, 127.5, 128.0, 128.7, 128.8, 129.6, 132.8, 143.2, 144.2, 149.1, 150.3, 160.8. Anal. Calcd. for $C_{25}H_{14}FN_3O$: C 76.72, H 3.61, N 10.74. Found: C 76.86, H 3.79, N 10.86.

3. Results and discussion

The chemistry of enamines and their derivatives has numerous attractive features that have made them important building blocks