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Synthesis of novel benzo[*b*]pyrimido[4′,5′:5,4]thieno[2,3-e][1,6]naphthyridine-8-ones *via* Pictet–Spengler cyclization

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ABSTRACT

An efficient method for the synthesis of novel benzo[*b*]pyrimido[4′,5′:5,4]thieno[2,3e]-[1,6]naphthyridine-8-one derivatives *via* Pictet–Spengler cyclization is reported. The reaction of 4-(3-aminopyrimido[4,5-d]thieno-2-yl)quinoline-2-ones, which could be obtained from Thorpe–Ziegler isomerization of 4-bromomethylquinoline-2-ones and 5-cyano-1,6-dihydro-4-methyl-2-phenyl-6-thioxopyrimidine, with aromatic aldehydes in the presence of $BF_3{\cdot}OEt_2$ gives pyrimidothieno[1,6]naphthyridines in good yields.

1. Introduction

1,6-Naphthyridine derivatives, nitrogen heterocycles containing two pyridine rings, are widely distributed in nature [1], and they are considered to be "privileged structures" in drug discovery. In particular, functionalized [1,6]naphthyridines and their benzo/hetero-fused analogues have displayed a wide range of physiological activities, such as anticancer [2], anti HIV-1 [3], antimicrobial [4] and cytotoxic activities [5]. Consequently, various methods havebeen reported for the synthesis of these compounds including multi component reactions [6], metal-catalyzed reactions [7], cycloaddition reactions [8] and other approaches [9].

The Pictet–Spengler reaction [10] has become one of the most prominent strategies for carbon–carbon bond formation in synthetic organic chemistry with excellent functional group tolerance, regio- and stereo-selectivity. From this perspective, the modified Pictet–Spengler reactions are attained considerable important for the synthesis of various products and novel heterocycles of biological interest [11].

In addition, pyrimidine derivatives and pyrimidine-fused compounds are of interest in medicinal chemistry and chemical biology due to their wide range of biological activities [12]. On account of the pharmaceutical interest in these compounds, the development of highthroughput methodologies for the synthesis of novel pyrimidine-fused heterocyclic scaffolds is in continuous expansion [13].

In our previous studies [14] we reported the synthesis of fused nitrogen-containing ring systems. As part of our program to develop new methods for the construction of important heterocycles using Pictet–Spengler reaction, herein, a convenient approach for the synthesis of novel benzo[*b*]pyrimido[4′,5′:5,4]thieno[2,3-e][1,6]naphthyridine derivatives from readily accessible 4-bromomethyl quinoline-2-one [15] using Pictet–Spengler reactions a key step is described (Scheme 1).

2. Experimental

2.1. Preparation of 4-(3-aminopyrimido[4,5-d]thieno-2-yl)quinoline-2-ones (*3*)

To a solution of 4-bromomethylquinoline-2-one **1** (20.0 mmol) in DMF (25 mL) was added 5-cyano-1,6-dihydro-4-methyl-2-phenyl-6-thioxopyrimidine **2** [16] (6.81 g, 30.0 mmol) and anhydrous potassium carbonate (5.52 g, 40.0 mmol). The mixture was heated at 80 °C for 5 h. After cooling to room temperature, water (50 mL) was added and stirred for 20 min. The solid was filtered and recrystallized from HOAc to give **3**.

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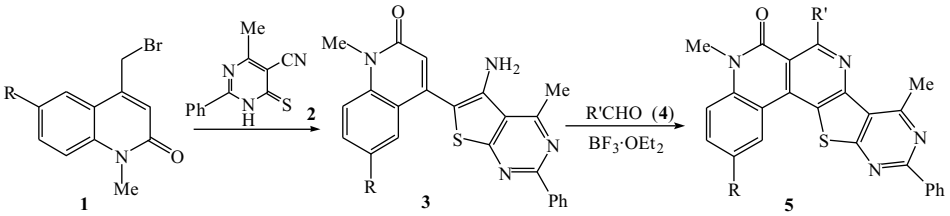

a R = Me, **b** R = OMe

Scheme 1. Syntheses of benzo[*b*]pyrimido[4′,5′:5,4]thieno[2,3-e][1,6]naphthyridine-8-ones.

3a: 82%. Mp > 300 °C. IR (KBr, cm^{-1}): ν 3403, 3373 (NH_2), 1686 (C=O). ^{1}H NMR (400 MHz, CF_3CO_2D): δ 2.51 (s, 3*H*), 3.01 (s, 3*H*), 4.27 (s, 3*H*), 7.67–7.70 (m, 3*H*), 7.77–7.81 (m, 2*H*), 7.97–7.99 (m, 2*H*), 8.25–8.30 (m, 2*H*). ^{13}C NMR (100 MHz, CF_3CO_2D): δ 16.8, 18.9, 32.3, 115.9, 116.7, 121.3, 123.7, 124.0, 125.8, 127.7, 128.1, 128.3, 129.5, 129.6, 134.9, 136.2, 137.2, 138.7, 139.8, 144.3, 154.7, 160.5. Anal. Calcd. for $C_{24}H_{20}N_4OS$: C 69.88, H 4.98, N 13.58, S 7.35. Found: C 69.97, H 5.14, N 13.73, S 7.46.

3b: 86%. Mp > 300 °C. IR (KBr, cm^{-1}): ν 3441, 3445 (NH_2), 1682 (C=O). ^{1}H NMR (400 MHz, CF_3CO_2D): δ 3.32 (s, 3*H*), 3.90 (s, 3*H*), 4.28 (s, 3*H*), 7.33 (s, 1*H*), 7.68–7.78 (m, 5*H*), 8.08–8.09 (m, 1*H*), 8.29–8.31 (m, 2*H*). ^{13}C NMR (100 MHz, CF_3CO_2D): δ 16.8, 32.5, 55.2, 107.9, 116.7, 118.6, 123.0, 123.7, 124.1, 127.7, 128.1, 128.3, 129.5, 129.6, 132.9, 135.0, 138.7, 143.6, 154.7, 158.6, 159.7. Anal. Calcd. for $C_{24}H_{20}N_4O_2S$: C 67.27, H 4.70, N 13.07, S 7.48. Found: C 67.38, H 4.85, N 13.15, S 7.59.

2.2. Preparation of benzo[b]pyrimido[4′,5′:5,4]thieno[2,3e][1,6]-naphthyridine-8-one derivatives

A mixture of 4-(3-aminopyrimido[4,5-d]thieno-2-yl)quinoline-2-one **3** (1.0 mmol), aromatic aldehyde **4** (1.0 mmol) and $BF_3{\cdot}OEt_2$ (14.2 mg, 0.1 mmol) in DMF (15 mL) was heated for 4–12 h at 100 °C. After the completion of the reaction judged by TLC analysis, the reaction mixture was cooled to room temperature. Water (30 mL) was added and the mixture was stirred for 30 min. The solid was filtered and recrystallized from DMF to afford the corresponding products (**5a–k**)[1].

[1] Physical and spectral (IR, NMR, Anal.) data:

5a: Mp > 300 °C. IR (KBr, cm^{-1}): ν 1670 (C=O). ^{1}H NMR (400 MHz, CF_3CO_2D): δ 2.69 (s, 3*H*), 3.38 (s, 3*H*), 3.75 (s, 3*H*), 7.44–7.45 (m, 1*H*), 7.56–7.58 (m, 7*H*), 7.71–7.72 (m, 2*H*), 8.59 (s, 1*H*), 8.67–8.69 (m, 2*H*). ^{13}C NMR (100 MHz, CF_3CO_2D): δ 21.2, 23.1, 30.4, 115.1, 116.8, 117.4, 121.5, 123.2, 127.4, 127.7, 128.0, 128.6, 128.8, 128.9, 131.2, 132.4, 132.9, 137.0, 137.9, 138.2, 143.2, 150.7, 159.9, 160.8, 162.4, 166.2, 170.6. Anal. Calcd. for $C_{31}H_{22}N_2OS$: C 74.68, H 4.45, N 11.24, S 6.43. Found: C 74.79, H 4.54, N 11.37, S 6.58.

5b: Mp > 300 °C. IR (KBr, cm^{-1}): ν 1674 (C=O). ^{1}H NMR (400 MHz, CF_3CO_2D): δ 2.51 (s, 3*H*), 2.66 (s, 3*H*), 3.43 (s, 3*H*), 3.77 (s, 3*H*), 7.36–7.38 (m, 2*H*), 7.44–7.46 (m, 1*H*), 7.58–7.64 (m, 6*H*), 8.62 (s, 1*H*), 8.69 (m, 2*H*). ^{13}C NMR (100 MHz, CF_3CO_2D): δ 19.1, 19.5, 30.9, 39.1, 112.2, 113.2, 114.9, 116.0, 116.8, 117.4, 118.7, 127.1, 127.4, 128.5, 129.0, 129.6, 129.8, 131.4, 131.9, 135.9, 137.2, 137.8, 138.5, 140.9, 143.9, 144.1, 157.3, 159.6. Anal. Calcd. for $C_{32}H_{24}N_4OS$: C 74.98, H 4.72, N 10.93, S 6.26. Found: C 75.14, H 4.86, N 11.08, S 6.42.

5c: Mp > 300 °C. IR (KBr, cm^{-1}): ν 1681 (C=O). ^{1}H NMR (400 MHz, CF_3CO_2D): δ 2.39 (s, 3*H*), 3.00 (s, 3*H*), 3.75 (s, 3*H*), 3.85 (s, 3*H*), 6.99–7.03 (m, 2*H*), 7.21–7.25 (m, 1*H*), 7.37–7.39 (m, 1*H*), 7.47–7.50 (m, 1*H*), 7.54–7.58 (m, 4*H*), 8.21 (s, 1*H*), 8.60–8.61 (m, 2*H*). ^{13}C NMR (100 MHz, CF_3CO_2D): δ 20.8, 23.8, 29.6, 55.4, 112.4, 114.5, 117.2, 118.5, 118.7, 122.1, 124.2, 125.2, 127.4, 128.5, 128.6, 128.8, 129.7, 130.6, 132.0, 132.5, 136.5, 137.4, 138.2, 141.5, 142.8, 159.8, 160.2, 161.1, 163.7, 167.3. Anal. Calcd. for $C_{32}H_{24}N_4O_2S$: C 72.71, H 4.58, N 10.60, S 6.07. Found: C 72.86, H 4.69, N 10.73, S 6.19.

5d: Mp > 300 °C. IR (KBr, cm^{-1}): ν 1684 (C=O). ^{1}H NMR (400 MHz, CF_3COOD): δ 2.67 (s, 3*H*), 3.34 (s, 3*H*), 4.09 (s, 3*H*), 7. 18–7.22 (m, 4*H*), 7.47–7.49 (m, 1*H*), 7.63–7.69 (m, 3*H*), 7.74–7.82 (m, 4*H*). ^{13}C NMR (100 MHz, CF_3COOD): δ 19.2, 30.8, 39.1, 112.2, 113.2, 115.0, 116.0, 116.5, 116.7, 117.0, 121.1, 126.4, 126.5, 127.9, 128.3, 128.6, 129.7, 129.8, 135.3, 135.4, 136.4, 136.5, 137.0, 137.9, 140.8, 156.5,161.6. Anal. Calcd. for $C_{31}H_{21}ClN_4OS$: C 69.85, H 3.97, N 10.51, S 6.02. Found: C 69.98, H 4.15, N 10.67, S 6.11.

3. Results and discussion

In this letter, we have presented a new and efficient method for the synthesis of benzo[*b*]pyrimido[4′,5′:5,4]thieno[2,3-e][1,6]naphthyridine-8-ones can be readily synthesized from 4-bromomethylquinoline-2-ones and 5-cyano-1,6-dihydro-4-methyl-2-phenyl-6-thioxopyrimidine, by using a Thorpe–Ziegler isomerization and Pictet–Spengler reaction (Scheme 1).

In this study, the key intermediate amine 4-(3-aminopyrimido[4,5-d]thieno-2-yl)quinoline-2-ones **3** was obtained by the

5e: Mp > 300 °C. IR (KBr, cm^{-1}): ν 1689 (C=O). ^{1}H NMR (400 MHz, CF_3COOD): δ 2.72 (s, 3*H*), 3.22 (s, 3*H*), 3.33 (s, 3*H*), 7.21–7.29 (m, 1*H*), 7.28–7.29 (m, 2*H*), 7.64–7.65 (m, 1*H*), 7.72–7.86 (m, 5*H*), 8.19–8.21 (m, 1*H*), 8.41–8.44 (m, 1*H*), 8.71 (s, 1*H*). ^{13}C NMR (100 MHz, CF_3CO_2D): δ 30.8, 33.3, 39.0, 112.2, 115.1, 115.4, 116.0, 116.5 (d, *J* = 23.5 Hz), 116.6, 117.1, 120.7 (d, *J* = 8.2 Hz), 126.5, 126.8, 127.8, 128.6, 129.7, 129.9, 130.7, 130.8, 135.4, 135.7, 136.6, 137.2, 141.4, 145.8 (d, *J* = 2.5 Hz), 156.6 (d, *J* = 243.4 Hz), 160.0. Anal. Calcd. for $C_{31}H_{21}FN_4OS$: C 72.08, H 4.10, N 10.85, S 6.21. Found: C 72.27, H 4.27, N 10.96, S 6.37.

5f: Mp > 300 °C. IR (KBr, cm^{-1}): ν 1672 (C=O). ^{1}H NMR (400 MHz, CF_3CO_2D): δ 4.06 (s, 3*H*), 4.13 (s, 3*H*), 4.27 (s, 3*H*), 7.28–7.31 (m, 2*H*), 7.82–7.86 (m, 5*H*), 7.92–7.96 (m, 3*H*), 8.45–8.44 (m, 3*H*). ^{13}C NMR (100 MHz, CF_3CO_2D): δ 31.2, 55.1, 55.6, 110.4, 112.2, 113.3, 114.4, 115.0, 116.1, 117.3, 117.6, 120.2, 122.8, 127.2, 127.8, 128.8, 129.8, 131.0, 134.4, 135.7, 141.9, 144.3, 156.8, 157.0, 160.2, 160.9, 161.4. Anal. Calcd. for $C_{31}H_{22}N_4O_2S$: C 72.35, H 4.31, N 10.89, S 6.23. Found: C 72.53, H 4.50, N 10.95, S 6.39.

5g: Mp > 300 °C. IR (KBr, cm^{-1}): ν 1678 (C=O). ^{1}H NMR (400 MHz, $CF_3CO_2D_3$): δ 3.53 (s, 3*H*), 3.65 (s, 3*H*), 4.28 (s, 3*H*), 4.51 (s, 3*H*), 7.87–7.92 (m, 3*H*), 8.03–8.05 (m, 4*H*), 8.15–8.21 (m, 2*H*), 8.70–8.74 (m, 3*H*). ^{13}C NMR (100 MHz, CF_3CO_2D): δ 31.1, 33.4, 39.0, 55.4, 110.3, 113.2, 117.3, 117.4, 118.5, 119.5, 121.9, 123.6, 126.1, 127.5, 128.0, 128.6, 128.9, 129.3, 129.4, 129.7, 133.0, 134.7, 135.8, 142.6, 143.3, 157.0, 157.2, 159.7. Anal. Calcd. for $C_{32}H_{24}N_4O_2S$: C 72.71, H 4.58, N 10.60, S 6.07. Found: C 72.86, H 4.74, N 10.72, S 6.15.

5h: Mp > 300 °C. IR (KBr, cm^{-1}): ν 1685 (C=O). ^{1}H NMR (400 MHz, CF_3CO_2D): δ 3.29 (s, 3*H*), 3.85 (s, 3*H*), 3.89 (s, 3*H*), 4.15 (s, 3*H*), 7.25–7.27 (m, 1*H*), 7.38–7.40 (m, 3*H*), 7.64–7.67 (m, 2*H*), 7.75–7.78 (m, 1*H*), 7.83–7.85 (m, 1*H*), 7.91–7.94 (m, 1*H*), 8.25–8.27 (m, 2*H*), 8.50–8.52 (m, 1*H*). ^{13}C NMR (100 MHz, CF_3CO_2D): δ 31.9, 32.2, 54.9, 55.0, 108.7, 114.4, 117.6, 118.5, 122.0, 122.2, 123.3, 124.1, 124.8, 127.8, 128.2, 128.5, 129.4, 129.5, 130.6, 132.6, 132.8, 134.8, 144.1, 144.2, 154.4, 158.4, 159.2, 160.1. Anal. Calcd. for $C_{32}H_{24}N_4O_3S$: C 70.57, H 4.44, N 10.29, S 5.89. Found: C 70.70, H 4.62, N 10.41, S 5.94.

5i: Mp > 300 °C. IR (KBr, cm^{-1}): ν 1688 (C=O). ^{1}H NMR (400 MHz, CF_3CO_2D): δ 2.19 (s, 3*H*), 3.33 (s, 3*H*), 4.10 (s, 3*H*), 4.15 (s, 3*H*), 7.04–7.07 (m, 2*H*), 7.15–7.18 (m, 2*H*), 7.64–7.73 (m, 4*H*), 7.91–7.92 (m, 1*H*), 8.19–8.22 (m, 1*H*), 8.25–8.27 (m, 1*H*), 8.39–8.41 (m, 1*H*). ^{13}C NMR (100 MHz, CF_3CO_2D): δ 31.5, 33.0, 39.5, 55.9, 110.7, 112.6, 113.6, 115.4, 116.4, 117.7, 118.1, 120.8, 122.8, 127.5, 128.1, 128.8, 128.9, 129.1, 130.1, 130.9, 134.6, 135.9, 138.3, 141.3, 141.6, 157.1, 157.2, 162.8. Anal. Calcd. for $C_{32}H_{24}N_4O_3S$: C 70.57, H 4.44, N 10.29, S 5.89. Found: C 70.68, H 4.56, N 10.43, S 5.97.

5j: Mp > 300 °C. IR (KBr, cm^{-1}): ν 1683 (C=O). ^{1}H NMR (400 MHz, CF_3CO_2D): δ 3.34 (s, 3*H*), 4.10 (s, 3*H*), 4.16 (s, 3*H*), 6.61–6.63 (m, 1*H*), 6.69–6.72 (m, 1*H*), 7.28–7.30 (m, 1*H*), 7.65–7.74 (m, 4*H*), 7.91–7.92 (m, 1*H*), 8.20–8.23 (m, 2*H*), 8.27–8.30 (m, 1*H*), 8.42–8.44 (m, 1*H*). ^{13}C NMR (100 MHz, CF_3CO_2D): δ 34.0, 55.0, 55.5, 107.6, 110.4, 115.0, 115.2, 117.2 (d, *J* = 23.2 Hz), 117.9, 118.2, 121.1 (d, *J* = 8.4 Hz), 121.5, 126.3, 127.9, 128.0, 128.6, 129.5, 129.7, 130.7, 130.8, 133.8, 135.3, 140.3, 147.0 (d, *J* = 2.3 Hz), 156.4, 156.6 (d, *J* = 243.1 Hz), 160.1. Anal. Calcd. for $C_{31}H_{21}FN_4O_2S$: C 69.91, H 3.97, N 10.52, S 6.02. Found: C 70.15, H 4.16, N 10.68, S 6.13.

5k: Mp > 300 °C. IR (KBr, cm^{-1}): ν 1692 (C=O). ^{1}H NMR (400 MHz, CF_3CO_2D): δ 3.39 (s, 3*H*), 4.10 (s, 3*H*), 4.16 (s, 3*H*), 6.57–7.65 (m, 5*H*), 7.75–7.77 (m, 1*H*), 7.89–7.90 (m, 1*H*), 8.09–8.12 (m, 2*H*), 8.21–8.27 (m, 3*H*). ^{13}C NMR (100 MHz, CF_3CO_2D): δ 31.4, 52.5, 55.4, 107.8, 112.1, 112.2, 113.2, 115.0, 116.1, 116.7, 118.7, 119.4, 121.7, 123.8, 127.5, 128.0, 129.5, 133.5, 134.6, 137.5, 141.3, 147.2, 148.1, 154.1, 156.7, 158.7, 159.6. Anal. Calcd. for $C_{31}H_{21}NO_4S$: C 66.54, H 3.78, N 12.51, S 5.73. Found: C 66.68, H 3.89, N 12.73, S 5.87.