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An efficient approach to the synthesis of coumarin-fused dihydropyridinones

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Abstract: 3,4-Dihydro-2*H*-chromeno[4,3-*b*]pyridine-2,5(1*H*)-dione derivatives were efficiently prepared by the reaction of 4-hydroxycoumarin, ammonia, aromatic aldehyde and Meldrum's acid in refluxing 1-propanol.

Keywords: functionalized coumarins; Meldrum's acid; one-pot reaction.

Introduction

The development of high yielding, efficient and reliable strategies is needed to access the manifolds of polycyclic reaction products for biological evaluation [1, 2]. Multi-component reaction (MCR) methodology is highly preferred over other synthetic methods, successfully providing a short synthetic pathway to desired products. The capability of this valuable synthetic approach has been considered by pharmaceutical companies for the large-scale synthesis of drugs [3–5].

In the field of medicinal chemistry, coumarin constitutes an exceptional structural framework in bioactive compounds [6–13] and an impressive number of synthetic methods [14–21] have been reported to enhance the collection of coumarin-containing molecules [22–25]. Fused bicyclic chromenes are of considerable interest. Such compounds are anti-cancer [26], glucocorticoid receptor agonist [27], anti-bacterial [28], anti-histaminic [29] and anti-myopic agents [30]. Following our focus on the synthesis of heterocyclic compounds [31–37], in the present paper, we report the convenient, four-component construction of 4-aryl-3,4-dihydro-2*H*-chromeno[4,3-*b*]pyridine-2,5(1*H*)-diones, starting from 4-hydroxycoumarin, ammonia, aldehyde and Meldrum's acid.

Results and discussion

The synthetic pathway is outlined in Scheme 1. In a model reaction, 4-hydroxycoumarin (**1**), aqueous ammonia (**2**), benzaldehyde (**3a**) and Meldrum's acid (**4**) were allowed to react in 1-propanol to furnish product **5a**. Under optimized conditions the reaction is conducted in boiling 1-propanol in the presence of five equivalents of ammonia. With ammonium acetate as a nitrogen source under otherwise similar conditions the yield of **5a** was only 45%, even after prolonged reflux. Under the optimized reaction conditions, different aromatic aldehydes were evaluated to examine the generality of the cyclization reaction. In the presence of electron-donating and electron-withdrawing substituents at the 2-, 3- and 4-positions of the phenyl ring the target compounds were obtained in good yields.

In the proposed mechanism (Scheme 2), the amination reaction of **1** leads to generation of 4-aminocoumarin **6** which then undergoes a Michael-type addition reaction to the intermediate product **7**. Compound **7** is a product of a Knoevenagel condensation reaction between the aromatic aldehyde and Meldrum's acid. The intramolecular cyclization process after the loss of acetone and CO_2 from the intermediate product **8** results in the formation of the final product **5** (Scheme 2). To confirm the reaction mechanism, the intermediate products **6** and **7** were prepared separately [38]. As expected, their reaction furnished the product **5**.

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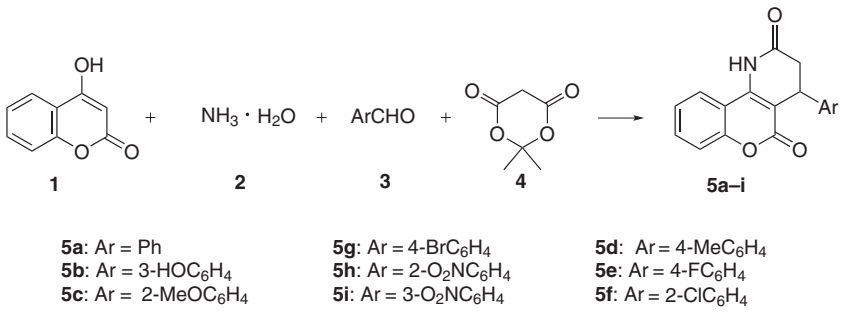
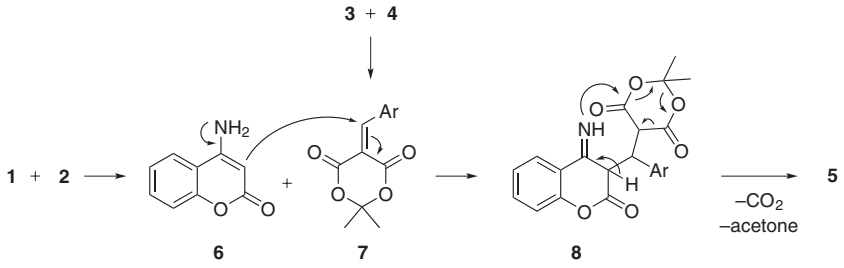


5a: Ar = Ph
5b: Ar = 3-HOC_6H_4
5c: Ar = 2-$MeOC_6H_4$
5d: Ar = 4-MeC_6H_4
5e: Ar = 4-FC_6H_4
5f: Ar = 2-ClC_6H_4
5g: Ar = 4-BrC_6H_4
5h: Ar = 2-$O_2NC_6H_4$
5i: Ar = 3-$O_2NC_6H_4$

Scheme 1



Scheme 2

Conclusions

An efficient and straightforward method was developed for the synthesis of 3,4-dihydro-1*H*-chromeno[4,3-*b*]pyridine-2,5-diones **5**. The method involves a simple, one-pot, four-component reaction.

Experimental

^{1}H nuclear magnetic resonance (NMR) (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained in DMSO-d_6. Infrared (IR) spectra were recorded in KBr pellets. Additional general information is described in reference [16].

General procedure for the synthesis of 3,4-dihydro-1*H*-chromeno[4,3-*b*]pyridine-2,5-diones 5a–i

A solution of 4-hydroxycoumarin (1 equiv.) and ammonia (30%, 5 equiv.) in 1-propanol (10 mL) was heated under reflux for 1 h, after which time, Meldrum's acid (1 equiv.) and aromatic aldehyde (1.1 equiv.) were added and the mixture was heated under reflux for an additional 12 h. Then the mixture was concentrated under a reduced pressure and the residue was purified on a silica gel column eluting with petroleum ether/ethyl acetate, 8:2.

4-Phenyl-3,4-dihydro-2*H*-chromeno[4,3-*b*]pyridine-2,5(1*H*)-dione (5a) Yield 68% of a pale yellow powder; mp 230°C (dec.); IR: 3287, 3038, 2905, 1715, 1678, 1625, 1517, 1458, 1365, 1278, 1196, 1160, 1002, 753 cm^{-1}; ^{1}H NMR: δ 3.03 (d, 1H, *J* = 16.5 Hz), 3.32 (dd, 1H, *J* = 16.5, 7.0 Hz), 4.59 (d, 1H, *J* = 7.0 Hz), 7.20–7.35 (m, 4H), 7.36–7.38 (m, 2H), 7.40 (d, 1H, *J* = 8.5 Hz), 7.61 (t, 1H, *J* = 8.0 Hz), 7.68 (d, 1H, *J* = 8.0 Hz), 8.86 (s, NH); ^{13}C NMR: δ 35.4, 37.8, 113.0, 116.7, 123.0, 124.1, 126.4, 126.9, 128.6, 132.3 (2C), 141.2, 145.4 (2C), 152.6, 170.1. Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.51; H, 4.32; N, 4.59.

4-(3-Hydroxyphenyl)-3,4-dihydro-2*H*-chromeno[4,3-*b*]pyridine-2,5(1*H*)-dione (5b) Yield 62% of a pale yellow powder; mp 230°C; IR: 3239, 1672, 1627, 1580, 1515, 1458, 1367, 1297, 764 cm^{-1}; ^{1}H NMR: δ 2.63 (d, 1H, *J* = 16.0 Hz), 3.22 (dd, 1H, *J* = 16.0, 8.0 Hz), 4.29 (d, 1H, *J* = 8.0 Hz), 6.60 (s, 1H), 6.62 (d, 1H, *J* = 8.0 Hz), 6.66 (d, 1H, *J* = 7.5 Hz), 7.09–7.11 (m, 2H), 7.41 (t, 1H, *J* = 7.5 Hz), 7.45 (d, 1H, *J* = 8.2 Hz), 7.68 (t, 1H, *J* = 7.5 Hz), 8.27 (d, 1H, *J* = 8.2 Hz), 9.44 (brs, NH); ^{13}C NMR: δ 35.4, 37.9, 103.5, 113.2, 116.8, 117.1, 122.9, 123.1, 124.2, 129.7, 132.0, 132.3, 142.6, 145.3, 152.6, 157.6, 160.1, 170.2. Anal. Calcd for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56. Found: C, 70.52; H, 4.03; N, 4.33.

4-(2-Methoxyphenyl)-3,4-dihydro-2*H*-chromeno[4,3-*b*]pyridine-2,5(1*H*)-dione (5c) Yield 64% of a pale yellow powder; mp 254°C; IR: 3254, 2963, 1725, 1633, 1517, 1490, 1245, 1196, 754 cm^{-1}; ^{1}H NMR: δ 2.53 (d, 1H, *J* = 16.1 Hz), 3.17 (dd, 1H, *J* = 16.1, 8.5 Hz), 3.84 (s, 3H), 4.58 (d, 1H, *J* = 8.5 Hz), 6.80 (t, 1H, *J* = 7.5 Hz), 6.86 (d, 1H, *J* = 7.5 Hz), 7.03 (d, 1H, *J* = 8.5 Hz), 7.23 (t, 1H, *J* = 7.5 Hz), 7.42–7.44 (m, 2H), 7.68 (t, 1H, *J* = 8.2 Hz), 8.26 (d, 1H, *J* = 8.5 Hz), 10.89 (s, NH); ^{13}C NMR: δ 30.8, 36.4, 55.2, 102.2, 111.2, 113.0, 116.7, 120.2, 123.0, 124.1, 126.6, 128.0, 128.3, 132.3, 146.2, 152.7, 156.5, 159.9, 170.1. Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 70.88; H, 4.93; N, 4.14.

4-(*p*-Tolyl)-3,4-dihydro-2*H*-chromeno[4,3-*b*]pyridine-2,5(1*H*)-dione (5d) Yield 71% of a pale yellow powder; mp 226°C; IR: 3233, 1727, 1691, 1570, 1459, 1365, 1317, 1293, 1195, 756 cm^{-1}; ^{1}H NMR: δ 2.25 (s, 3H), 2.63 (d, 1H, *J* = 16.5 Hz), 3.22 (dd, 1H, *J* = 16.5, 7.2 Hz), 4.33 (d,

1H, J = 7.2 Hz), 7.09–7.11 (m, 4H), 7.40 (t, 1H, J = 7.5 Hz), 7.44 (d, 1H, J = 8.2 Hz), 7.67 (t, 1H, J = 7.5 Hz), 8.25 (d, 1H, J = 7.5 Hz), 10.93 (s, NH); ^{13}C NMR: δ 20.4, 35.1, 37.9, 103.6, 113.0, 116.7, 123.0, 124.1, 126.3, 129.2, 132.3, 136.0, 138.2, 145.2, 152.6, 160.1, 170.2. Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.59; H, 5.10; N, 4.40.

4-(4-Fluorophenyl)-3,4-dihydro-2*H*-chromeno[4,3-*b*]pyridine-2,5(1*H*)-dione (5e) Yield 70% of a pale yellow powder; mp 208°C; IR: 3393, 3135, 1718, 1688, 1629, 1566, 1456, 1368, 768 cm^{-1}; ^{1}H NMR: δ 2.67 (d, 1H, J = 16.3 Hz), 3.26 (dd, 1H, J = 16.3, 7.5 Hz), 4.40 (d, 1H, J = 7.5 Hz), 7.13 (t, 2H, J = 8.5 Hz), 7.27 (t, 2H, J = 6.5 Hz), 7.42 (t, 1H, J = 7.5 Hz), 7.45 (d, 1H, J = 8.5 Hz), 7.68 (t, 1H, J = 7.5 Hz), 8.27 (d, 1H, J = 7.5 Hz), 11.02 (s, NH); ^{13}C NMR: δ 34.8, 37.9, 103.3, 113.1, 116.7 (d, J_{C-F} = 20 Hz), 123.1 (d, J_{C-F} = 8 Hz), 124.1, 124.3, 128.4, 128.6, 132.4, 137.4, 145.5, 152.7, 160.2 (d, J_{C-F} = 243 Hz), 170.2. Anal. Calcd for $C_{18}H_{12}FNO_3$: C, 69.90; H, 3.91; N, 4.53. Found: C, 69.73; H, 4.09; N, 4.72.

4-(2-Chlorophenyl)-3,4-dihydro-2*H*-chromeno[4,3-*b*]pyridine-2,5(1*H*)-dione (5f) Yield 66% yield of a pale yellow powder; mp 244°C; IR: 3243, 1720, 1634, 1569, 1514, 1462, 1363, 1200, 1176, 1002, 762 cm^{-1}; ^{1}H NMR: δ 2.54 (d, 1H, J = 16.5 Hz), 3.32 (dd, 1H, J = 16.5, 8.2 Hz), 4.71 (d, 1H, J = 8.2 Hz), 7.02 (d, 1H, J = 7.3 Hz), 7.21 (t, 1H, J = 7.5 Hz), 7.29 (t, 1H, J = 7.5 Hz), 7.43–7.47 (m, 2H) 7.52 (d, 1H, J = 8.2 Hz), 7.70 (t, 1H, J = 7.5 Hz), 8.29 (d, 1H, J = 8.2 Hz), 11.07 (s, NH); ^{13}C NMR: δ 33.3, 36.4, 101.9, 113.0, 116.9, 123.2, 124.2, 127.2, 127.7, 129.0, 130.0, 132.4, 132.5, 137.6, 146.8, 152.8, 160.0, 169.5. Anal. Calcd for $C_{18}H_{12}ClNO_3$: C, 66.37; H, 3.71; N, 4.30. Found: C, 66.18; H, 3.54; N, 4.51.

4-(4-Bromophenyl)-3,4-dihydro-2*H*-chromeno[4,3-*b*]pyridine-2,5(1*H*)-dione (5g) Yield 75% of a pale yellow powder; mp 170°C; IR: 3223, 1721, 1691, 1632, 1515, 1461, 1365, 759 cm^{-1}; ^{1}H NMR: δ 2.64 (d, 1H, J = 16.3 Hz), 3.25 (dd, 1H; overlapping with the solvent signal), 4.37 (d, 1H, J = 7.5 Hz), 7.19 (d, 2H, J = 8.2 Hz), 7.38–7.55 (m, 4H), 7.69 (t, 1H, J = 7.5 Hz), 8.26 (d, 1H, J = 7.5 Hz), 11.02 (s, NH); ^{13}C NMR: δ 35.0, 37.6, 102.9, 113.0, 116.7, 120.1, 123.1, 128.8, 130.7, 131.7, 132.5, 140.7, 145.7, 152.7, 160.1, 170.1. Anal. Calcd for $C_{18}H_{12}BrNO_3$: C, 58.40; H, 3.27; N, 3.78. Found: C, 58.23; H, 3.06; N, 4.01.

4-(2-Nitrophenyl)-3,4-dihydro-2*H*-chromeno[4,3-*b*]pyridine-2,5(1*H*)-dione (5h) Yield 67% of a pale yellow powder; mp 244°C; IR: 3250, 3042, 1718, 1635, 1572, 1460, 1340, 1296, 855, 762 cm^{-1}; ^{1}H NMR: δ 2.68 (d, 1H, J = 16.5 Hz), 3.50 (dd, 1H, J = 16.5, 8.5 Hz), 4.79 (d, 1H, J = 8.5 Hz), 7.34 (d, 1H, J = 7.5 Hz), 7.48–7.51 (m, 2H), 7.57 (t, 1H, J = 7.2 Hz), 7.65 (t, 1H, J = 7.1 Hz), 7.75 (t, 1H, J = 7.5 Hz), 8.05 (d, 1H, J = 7.5 Hz), 8.36 (d, 1H, J = 7.5 Hz), 11.21 (s, NH); ^{13}C NMR: δ 31.9, 37.1, 102.0, 113.0, 117.1, 123.4, 125.0, 127.9, 128.2, 128.9, 132.7, 134.0, 135.4, 146.7, 148.6, 152.8, 160.0, 169.4. Anal. Calcd for $C_{18}H_{12}N_2O_5$: C, 64.29; H, 3.60; N, 8.33. Found: C, 64.06; H, 3.47; N, 8.11.

4-(3-Nitrophenyl)-3,4-dihydro-2*H*-chromeno[4,3-*b*]pyridine-2,5(1*H*)-dione (5i) Yield 74% of a pale yellow powder; mp 244°C; IR: 3277, 3091, 1715, 1678, 1524, 1459, 1349, 1277, 762 cm^{-1}; ^{1}H NMR: δ 2.74 (d, 1H, J = 16.3 Hz), 3.32 (dd, 1H, J = 16.3, 8.5 Hz), 4.57 (d, 1H, J = 8.5 Hz), 7.43 (t, 1H, J = 7.5 Hz), 7.46 (d, 1H, J = 8.2 Hz), 7.61 (t, 1H, J = 8.2 Hz), 7.69–7.70 (m, 3H), 8.11 (s, 1H), 8.28 (d, 1H, J = 8.5 Hz), 11.09 (s, NH); ^{13}C NMR: δ 35.2, 37.3, 102.4, 113.0, 116.9, 121.4, 122.1, 123.2, 124.2, 130.3, 132.6, 133.3, 143.6, 145.9, 148.1, 152.8, 160.1, 169.9. Anal. Calcd for $C_{18}H_{12}N_2O_5$: C, 64.29; H, 3.60; N, 8.33. Found: C, 64.51; H, 3.37; N, 8.15.

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