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A FACILE ONE-POT SYNTHESIS OF CHROMENO[4,3-*b*][1,5]-NAPHTHYRIDINES

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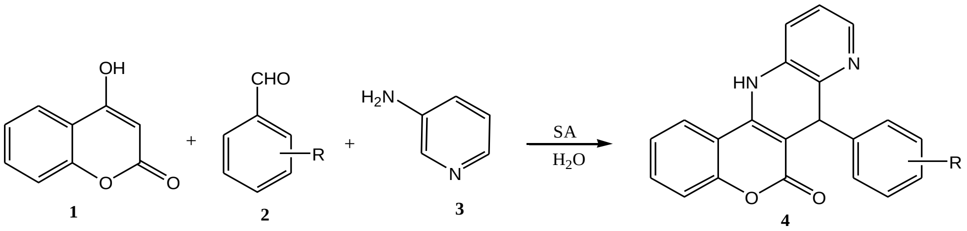
Abstract – A simple and efficient synthesis of chromeno[4,3-*b*][1,5]naphthyridine derivatives were accomplished in high yields *via* the one-pot three-component reaction of 4-hydroxycoumarin, arylaldehyde and 3-aminopyridine in aqueous media catalyzed by sulfamic acid.

Naphthyridines and their polycyclic derivatives are an important pharmacophore present in many natural[1] and designed synthetic products of therapeutic applications. They are associated with a wide spectrum of biological activities such as anticancer,[2] anti-HIV-1,[3] and cytotoxic activity.[4] Therefore, there has been increasing interest in developing facile methodologies for synthesis of naphthyridine framework of medicinal relevance.[5]

On the other hand, the coumarin moiety is abundant in various natural and synthetic products and has applications in both medicinal chemistry and optoelectronics.[6] Coumarin-fused polycyclic heterocyclic molecules have very interesting properties and therefore the development of new methods for facile accessto these molecules has received much attention.[7] 4-Hydroxycoumarin is one of the most widely explored and readily available substrates in organic synthesis.[8]

As part of our current studies on the development of new routes to heterocyclic systems,[9] we now report an efficient and clean synthetic method for the synthesis of chromeno[4,3-*b*][1,5]naphthyridines in aqueous media catalyzed by sulfamic acid (SA) (Scheme 1).



Scheme 1. Synthesis of chromeno[4,3-*b*][1,5]naphthyridines

When the reaction of 4-hydroxycoumarin **1**, arylaldehyde **2**, and 3-aminopyridine **3** was performed in water in the presence of SA at 100 °C, high yields of chromeno[4,3-*b*][1,5]naphthyridine derivatives **4** were obtained and representative examples are shown in Table **1**.

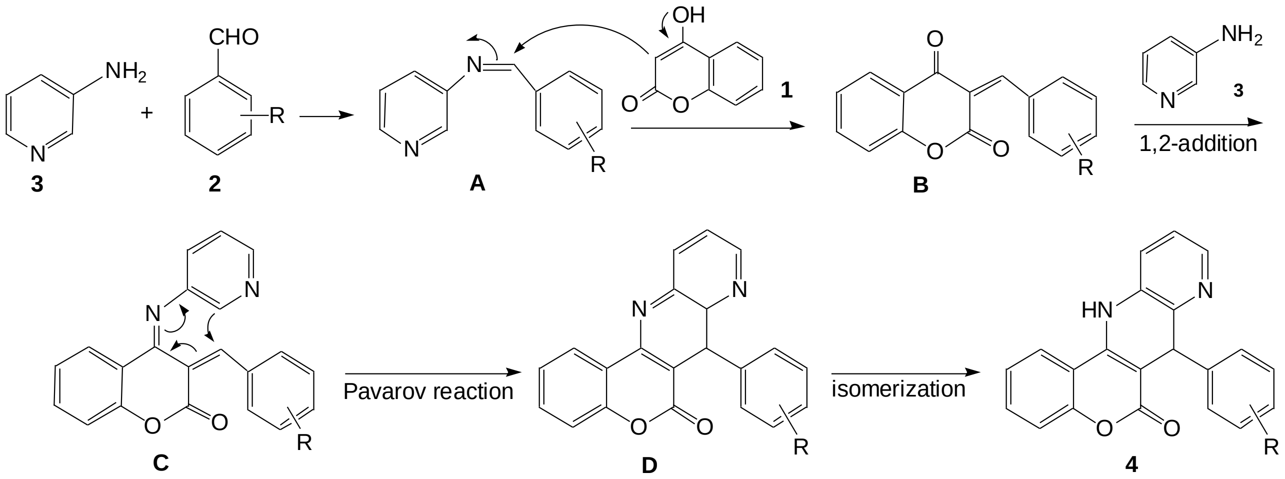
The effect of electrons and the nature of substituents on the aromatic ring did not show obvious effects in terms of yields under this reaction condition. The reaction proceeded smoothly under refluxing water to give the corresponding products **4** in high yields. Benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as halogen, nitro group) or electron-donating groups (such as methyl, methoxy, and hydroxy group) were employed and reacted well to give the corresponding chromeno-[4,3-*b*][1,5]naphthyridine derivatives in good to excellent yields.

Table 1. Synthesis of chromeno[4,3-*b*][1,5]naphthyridines **4**[10]

Entry	**2** / R		Time / h	Product	Yield / %
1	**2a**	H	7	**4a**	84
2	**2b**	4-Me	6	**4b**	86
3	**2c**	2-MeO	6	**4c**	81
4	**2d**	3-MeO	7	**4d**	85
5	**2e**	4-MeO	6	**4e**	91
6	**2f**	3,4-$(MeO)_2$	5	**4f**	90
7	**2g**	3,4,5-$(MeO)_3$	5	**4g**	92
8	**2h**	4-HO	8	**4h**	88
9	**2i**	2-F	9	**4i**	82
10	**2j**	4-F	8	**4j**	85
11	**2k**	4-Cl	9	**4k**	85
12	**2l**	4-NO_2	9	**4l**	78

The products **4** were completely characterized by IR, NMR, and elemental analyses. The analyses were in agreement with their structures. The IR spectra for **4a** exhibited sharp bands at 3356 cm^{-1} (NH) and 1657 cm^{-1} (C=O). The ^{1}H NMR spectrum of **4a** exhibited a singlet identified methane (6.32) along with multiplets (7.10~7.86) for aromatic protons. The NH proton resonance at 7.88 disappeared after addition of D_2O to the DMSO-d_6 solution of **4a**.

We proposed the following reaction mechanism for this reaction (Scheme 2). First, an imine **A** is formed via condensation of aldehyde **2** with 3-aminopryidine **3**. Then Povarov reaction of the 4-hydroxycoumarin moiety with the imine **A** to give a cyclized intermediate **C**. Subsequently, double bond isomerization furnishes the final product **4**.



Scheme 2. Proposed mechanism for the synthesis of compounds **4**

In summary, we have successfully developed an efficient green chemistry method for the synthesis of chromeno[4,3-*b*][1,5]naphthyridines *via* the one-pot three-component reaction. This method has the advantages of high yields, mild reaction conditions, easy work-up, inexpensive reagents and environmentally friendly procedure.

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10. The general procedure is represented as follow: A suspension of a mixture of 4-hydroxycoumarin **1** (1 mmol), arylaldehyde **2** (1 mmol), 3-aminopyridine **3** (1 mmol) and SA (20 mg, 0.2 mmol) was stirred in water (20 mL) at 100 °C. After completion monitored by TLC, the reaction mixture was allowed to cool to room temperature. The crystalline power formed recrystallized from DMF to give pure **4** (yield of the products is summarized in Table 1). Selected data of compound. **4a**: mp 246-248 °C; IR (KBr): v 3356 (NH), 1657 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.32 (1H, s), 7.10-7.19 (3H, m), 7.28-7.30 (2H, m), 7.32-7.34 (4H, m), 7.54-7.56 (2H, m), 7.86 (1H, d, J = 8.0 Hz), 7.88 (1H, s). ^{13}C NMR (100MHz, DMSO-d_6): δ 36.0, 104.5, 116.3, 118.7, 124.0, 124.3, 127.0, 129.0, 132.2, 134.7, 137.5, 152.7, 162.7, 165.2, 166.0. *Anal.* Calcd for $C_{21}H_{14}N_2O_2$: C 77.29, H 4.32, N 8.58. Found: C 77.37, H 4.43, N 8.65. **4b**: mp 279-281°C; IR (KBr): v 3363 (NH), 1651 cm^{-1} (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (3H, s, CH_3), 6.30 (1H, s), 7.03 (4H, m), 7.31-7.38 (4H, m), 7.58-7.62 (2H, m), 7.88 (1H, s), 7.89-7.91 (1H, m). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.0, 36.0, 104.5, 116.3, 118.7, 124.0, 124.3, 127.0, 129.0, 132.2, 134.7, 137.5, 152.7, 162.7, 165.2, 166.0. *Anal.* Calcd for $C_{22}H_{16}N_2O_2$: C 77.63, H 4.74, N 8.23. Found: C 77.72, H 4.79, N 8.34. **4d**: mp 265-267 °C; IR (KBr): v 3362 (NH), 1652 cm^{-1} (C=O). ^{1}H NMR (400MHz, DMSO-d_6): δ 3.64 (3H, s, OCH_3), 6.30 (1H, s), 6.65 (1H, s), 6.72-6.74 (2H, m), 7.13 (1H, t, J = 8.0Hz), 7.28-7.35 (4H, m), 7.56-7.60 (2H, m), 7.88 (1H, s), 7.89-7.90 (1H, m). ^{13}C NMR (100MHz, DMSO-d_6): δ 36.4, 55.2, 104.2, 110.0, 110.2, 113.7, 116.2, 119.1, 119.6, 123.9, 124.4, 129.4, 132.0, 152.7, 159.5, 165.1, 166.6. *Anal.* Calcd for $C_{22}H_{16}N_2O_3$: C 74.15, H 4.53 N 7.86. Found: C 74.27, H 4.66, N 7.94. **4j**: mp 268-270 °C; IR (KBr): v 3372 (NH), 1663 cm^{-1} (C=O). ^{1}H NMR (400MHz, DMSO-d_6): δ 6.31 (1H, s), 7.16-7.18 (2H, m), 7.26-7.38 (6H, m), 7.57-7.62 (2H, m), 7.87 (1H, s), 7.90-7.91 (1H, m). ^{13}C NMR (100MHz, DMSO-d_6): δ 36.1, 104.2, 116.3, 118.6, 124.1, 124.4, 128.3, 129.1, 130.4, 132.2, 140.0, 152.7, 165.0, 166.2. *Anal.* Calcd for $C_{21}H_{13}ClN_2O_2$: C 69.91, H 3.63, N 7.76. Found: C 69.98, H 3.69, N 7.85.