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Synthesis of 5*H*-Chromeno[4,3-*b*]pyridin-5-one derivatives as a backbone of natural product polyneomarline C scaffolds in presence of Et_3N and NH_4OAc in EtOH

Shrishnu Kumar Kundu [a*], Susanta Patra [b], Chayan Sardar [c], Sunil Kumar Bhanja [d], Prasanta Patra [b*]

a: Department of Chemistry, Acharya Prafulla Chandra Roy Government College, Siliguri 734 010, India
b: Department of Chemistry, Jhargram Raj College, Jhargram 721507, India
c: Techno-India University, Kolkata 700091, India
d: Government General Degree College, Kharagpur-II, Paschim Medinipur, India
* Corresponding authors: shrishnuk@gmail.com (S.K. Kundu); prasantaanupama1983@gmail.com (P. Patra)

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Abstract

A green one-pot synthesis of 5*H*-Chromeno[4,3-*b*]pyridin-5-one derivatives which are the main core of the natural product of Polyneomarline C is described by the reaction of 4-chloro-3-formyl coumarin and different cyclic and acyclic compounds having active methylene group in presence of Et_3N and NH_4OAc in EtOH. The advantages of this strategy are good yields, no need for the chromatographic separation and the absence of heavy metal catalysts and toxic by-products. The 4-chloro-3-formyl coumarin is obtained by Vilsmeier Heck reaction of 4-hydroxy coumarin.

Keywords

5*H*-Chromeno[4,3-*b*]pyridin-5-one
green synthesis
4-chloro-3-formyl coumarin
active methylene group
Polyalthia nemoralis C

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1. Introduction

In the last one or two decades, one-pot tandem chemical transformation without metal catalysts has been widely used for the synthesis of complex organic molecules. A variety of chemical conversion processes, such as oxidation, reduction, substitution, condensation, etc., has been developed using this principle [1–3]. A reaction undergoing without using toxic reagents (catalysts and solvents) has many advantages: a decrease of wastes, lower toxicity, maximum efficacy, a decrease in the energy requirements of the reactions, a possibility of designing biodegradable products, economic and time factors. Hence, heterocyclic ring formation using this green protocol is an active and attractive field. Coumarin derivatives represent the core structure of many naturally occurring compounds with significant biological activities [4–7]. Lamellarins and related pyrrole derived alkaloids isolated from diverse marine organisms are well known for their remarkable biological activities [8, 9]. The coumarin derivatives fused with azaheterocycles specially the pyridine nucleus have been reported to possess antiallergic, antidiabetic and analgesic properties [10–12]. Santiagonamine is a naturally occurring pyridine fused coumarin derivatives found in the stems and branches of Berberisdarwinii Hook, which is a shrub that abounds in South America having wound-healing properties [13, 14]. Goniothaline [15] is another a natural pyridocoumarin alkaloid, isolated from the Australian rainforest plant Goniothalamusaustralis, having antimalarial activity against a chloroquine-sensitive Plasmodium falciparum line (3D7). Polyneomarline C [16] is also a natural 6H-chromeno[4,3-*b*]quinolin-6-one derivative, isolated from the *Polyalthia nemoralis* A. DC, used as Chinese herbal medicine. Coumarin fused pyridine [17–19] derivatives have been reported to possess anti-hypertensive activities, anti-HIV activity, androgen receptor antagonist activity, and optoelectronic activity; they can also act as fluorescent dyes. All these observations highlight the importance and bioactivity of pyridine fused coumarin derivatives. So the interest towards the synthesis of pyridine fused comarin is trending among the organic chemists. Many methods [20–30] have been developed to synthesize these types of compounds using different types of Lewis acids/bases and metal catalysts with different solvents. The 5*H*-Chromeno[4,3-*b*]pyridin-5-one skeleton constitutes the backbone of Polyneomarline C. We were interested in the preparation of some non-natural analogs of this type of compounds by an easy process. Many synthese of 5*H*-Chromeno[4,3-*b*]pyridin-5-one derivatives have been de-

scribed in the literature [31, 32] using different reagents, catalyst, solvents and ultrasound irradiation. In our present work, we reported a modified green approach for the synthesis of 5*H*-Chromeno[4,3-*b*]pyridin-5-one derivatives from 4-chloro-3-formyl coumarin and various compounds having an active methylene group. In this method there is no need for the chromatographic separation.

2. Experimental

2.1. Preparation of substituted pyridocoumarin derivatives

A mixture of chloroaldehyde **1** of 4-hydroxy coumarin (1 mmol), **2** (1.2 mmol), Et_3N (1–2 drops) and NH_4OAc (2 mol%) with 10 ml EtOH was taken in 50 mL r.b. The mixture was then heated on an oil bath at 60 °C for 2 h. It was then cooled to room temperature. Then solvent was distilles out and residue was mixed with 20 mL water and filtered and washed with water and dried. The crude product which was purified by recrystalisation with EtOH to furnish compound **3**.

2.1.1. 3-acetyl-2-methyl-5*H*-chromeno[4,3-*b*]pyridin-5-one (3a)

Light pink solid, yield, 90%; mp 220–221 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): 2.62 (*s*, 3H), 2.68 (*s*, 3H), 7.42 (*m*, 1H), 7.52 (*d*, 1H, *J* = 7.8 Hz), 7.65 (*d*, 1H, *J* = 7.8 Hz), 7.79 (*m*, 1H), 9.33 (*s*, 1H); HRMS (ESI, 70 eV): *m*/*z* = 254.0820 (M^++H) [Calcd mass for $C_{15}H_{12}NO_3$: 254.0817 (M^++H)].

2.1.2. Ethyl 2-methyl-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carboxylate (3b)

Light pink solid, yield, 82%; mp 230–231 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): 1.3 (*t*, 3H, *J* = 7.2 Hz) 2.62 (*s*, 3H), 4.8 (*m*, 2H), 7.30–7.33 (*m*, 1H), 7.65 (*m*, 1H), 7.92 (*d*, 1H, *J* = 7.2 Hz), 7.78–7.80 (*m*, 1H), 8.90 (*s*, 1H); HRMS (ESI, 70 eV): *m*/*z* = 284.0929 (M^++H) [Calcd mass for $C_{16}H_{14}NO_4$: 284.0923 (M^++H)].

2.1.3. 10,11-Dihydro-9*H*-chromeno[4,3-*b*]quinoline-6,8-dione (3c)

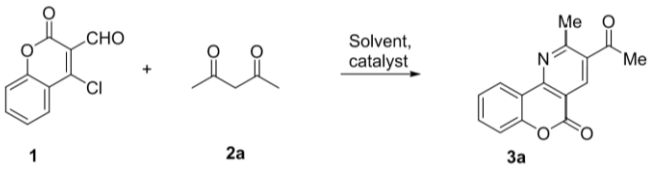
Light yellow solid, yield, 92%; mp 221–222 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): 1.98 (*m*, 2H), 2.45 (*t*, 2H, *J* = 7.2 Hz) 2.95 (*m*, 2H), 7.35 (*m*, 2H), 7.65–7.80 (*m*, 1H), 8.03 (*d*, 1H, *J* = 7.5 Hz), 9.22 (*s*, 1H) ppm; HRMS (ESI, 70 eV): *m*/*z* = 266.0821 (M^++H) [Calcd mass for $C_{16}H_{12}NO_3$: 266.0817 (M^++H)].

2.1.4. 9,9-Dimethyl-10,11-dihydro-9*H*-chromeno[4,3-*b*]quinoline-6,8-dione (3d)

Light yellow solid, yield, 85%; mp 239–240 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): 1.38 (*s*, 6H), 1.91 (*t*, 2H, *J* = 7.8 Hz), 2.92–2.95 (*m*, 2H), 7.45 (*t*, 2H, *J* = 8.0 Hz), 7.7 (*t*, 1H, *J* = 7.7 Hz), 8.13 (*dd*, 1H, *J* = 2.2 and 9.0 Hz), 9.33 (*s*, 1H) ppm; ^{13}C NMR (^{13}C NMR 100 MHz, DMSO-d_6): 23.2 (2), 28.2, 32.9, 113.3, 117.2, 117.9, 123.8, 125.32, 125.6, 125.7, 127.3, 136.33, 153.0, 154.0, 160.5, 169.8, 196.7; HRMS (ESI, 70 eV): *m*/*z* = 294.1121 (M^++H) [Calcd mass for $C_{18}H_{16}NO_3$: 294.1130 (M^++H)].

3. Results and discussion

Our first task was to find out an optimal condition to prepare the 5*H*-Chromeno[4,3-*b*]pyridin-5-one derivatives in the best possible yield using different methodologies. A reaction between 4-chloro-3-formyl coumarin (1 equivalent) and acetyl acetone (1.2 equivalent) (Scheme 1) was studied under different conditions with different temperatures and times (Table 1). When 3-formyl 4-chloro coumarin, which was obtained from 4-hydroxy coumarins [33], was treated with different cyclic and acyclic compounds having active methylene group in the presence of Et_3N and NH_4OAc in EtOH at 60 °C, within 2 h the corresponding 5*H*-Chromeno[4,3-*b*]pyridin-5-one derivatives were obtained. The ^{1}H-NMR (400 MHz, DMSO-d_6) data is in conformity with the assigned structure for the 5*H*-Chromeno[4,3-*b*]pyridin-5-one derivatives. A reaction of the other cyclic and acyclic compounds having an active methylene group **2(b-d)** and 4-chloro 3-formyl coumarin (1 equivalent) under identical condition produced the 5*H*-Chromeno[4,3-*b*]pyridin-5-one derivatives **3(a-d)**, respectively, in excellent yields (Scheme 2).

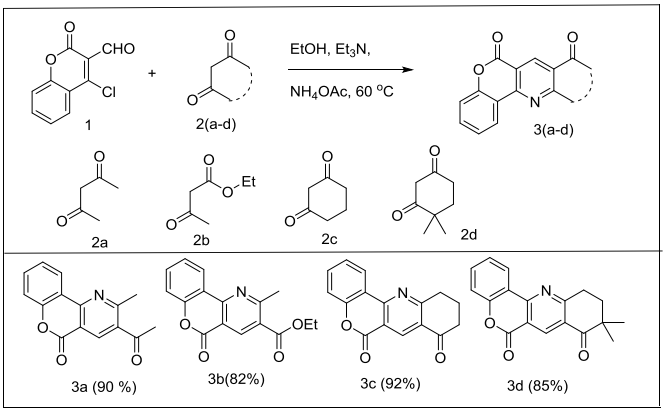


Scheme 1 Synthesis of pyridocoumarin by condensation followed by cyclization reaction.

Table 1 Optimization Studies in the formation of pyridocoumarin derivatives.[a]

Entry	Reactant proportions (1:2a)	Solvent	Catalysts	Additives	Temp. (°C)	Time (h)	Yields (%)
1	1:1	H_2O	–	–	100	10	--
2	1:2	H_2O	Et_3N	NH_4OAc	100	10	trace
3	1:1	EtOH	Et_3N	NH_4OAc	100	3	75
4	1:1	EtOH	Et_3N	NH_4OAc	60	2	90
5	1:1	EtOH	Et_3N	NH_4OAc	60	1	80
6	1:1	MeOH	Et_3N	NH_4OAc	80	5	40
7	1:1	EtOH	$NaHCO_3$	NH_4OAc	100	5	trace
8	1:1	DMF	Et_3N	NH_4OAc	100	2	trace
9	1:1	EtOH/H_2O	Et_3N	NH_4OAc	100	2	45
10	1:1	–	–	NH_4OAc	100	1	trace

[a] Reaction conditions: 4-Chloro 3-formyl coumarin **1** (1 mmol), **2a** (1.2 mmol), solvent (10 ml); Et_3N (cat), NH_4OAc (2 mmol), 60 °C.



Scheme 2 Substrate scope of for the synthesis of **3(a-d).**

Unfortunately, we did not have access to any other coumarin derivatives, but we believe our method will be applicable for other derivatives.

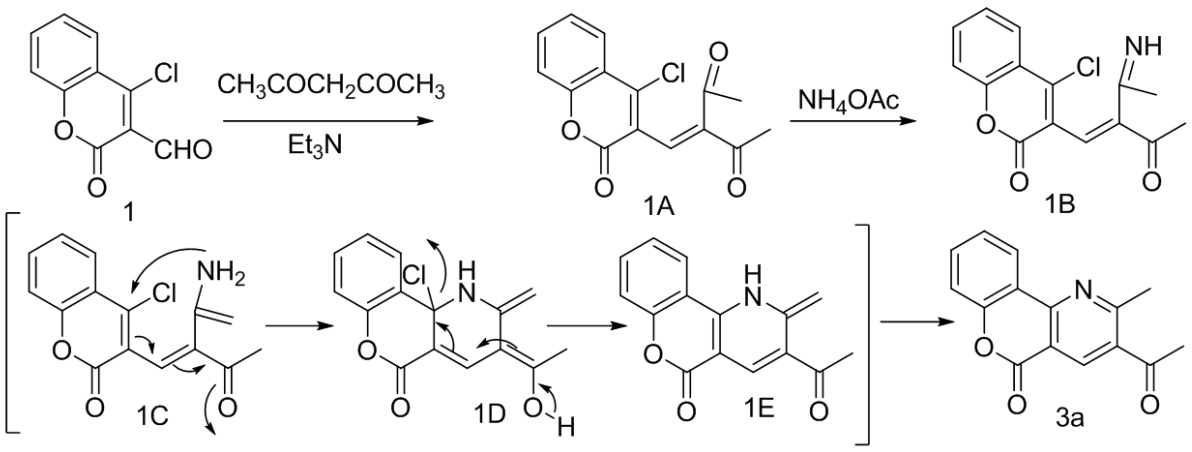
A probable mechanism for the formation of compounds **3a** is given in Scheme 3. In general, the reactions are very clean, proceeding without any side product, with remarkable yields, and do not requiring any chromatographic separation. Recrystallization from EtOH provides an analytically pure sample. We believe that it is the first green approach reported for the synthesis of fused 5H-Chromeno[4,3-b]pyridin-5-one derivatives.

4. Conclusions

In conclusion, we achieved the synthesis of poly-substituted pyridocoumarin derivative in one-pot three-component condensation and cyclization via an efficient, short and easy method. The method has a number of advantages: easy availability of the starting material, short time of the reaction, and the use of simple and inexpensive catalyst. We are planning a collaborative study into the photophysical and biological properties of the synthesized compounds in the near future.

Supplementary materials

No supplementary materials are available.



Scheme 3 Probable mechanism for the formation of pyridocoumarin derivatives.

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Author contributions

Conceptualization: S.K.K., P.P.
Data curation: S.P., C.S., S.K.B.
Formal Analysis: S.K.K., C.S.
Funding acquisition: P.P.
Investigation: S.K.K., P.P.
Methodology: S.P., C.S., S.K.B.
Project administration: P.P.
Resources: S.K.K.
Software: S.P.
Supervision: S.K.K., P.P.
Validation: S.K.K.
Visualization: P.P.
Writing – original draft: S.P.
Writing – review & editing: S.K.K., P.P.

Conflict of interest

The authors declare no conflict of interest.

Additional information

Author IDs:
Shrishnu Kumar Kundu, Scopus ID 15128586000;
Prasanta Patra, Scopus ID 36182642900.

Websites:

Acharya Prafulla Chandra Roy Government College, http://apcrgc.org/dept_chemistry/;

Jhargram Raj College, https://jrc.ac.in/;

Techno-India University, https://technoindia-group.com/;

Government General Degree College, http://singur-govtcollege.org/.

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