SYNTHESIS OF SOME NOVEL ANNULATED COUMARINS BY EXPLORING INTRAMOLECULAR HETERO DIELS ALDER REACTION STRATEGY

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Abstract: Some novel pyridocoumarin derivatives were synthesized from 4-hydroxycoumarins by exploring Diels Alder reaction strategy.

Keywords: 4-hydroxycoumarin; pyridocoumarins; Diels-Alder reaction

1. Introduction:

Coumarins are an important class of naturally occurring compounds which have diverse pharmaceutical and biological activities depending on the substituent in the benzopyran ring [1]. Among those, pyridine fused coumarin derivatives have drawn remarkable attention due to their varied biological activities like DNA adduct formation [2], energy transfer in photophysical processes [3], antitumor [4], anticholinergic [5], antidiabetic, anticoagulant, antiallergic, analgesic, antipsychotic [6], hypotensive activators [7], and antimicrobial [8] activities (**Fig-1**).

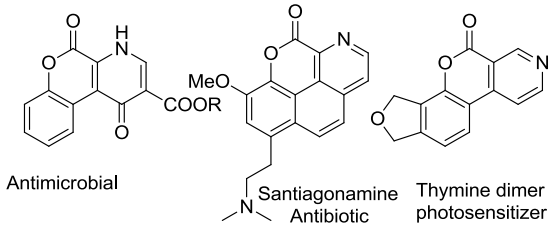


Figure 1: Some biologically important coumarins.

Therefore, considerable efforts have been made towards the preparation and synthetic manipulation of pyridocoumarin.

Cycloaddition reactions are one of the most useful reactions in synthetic and mechanistic organic chemistry [9]. Diels Alder reactions involve cyclic electron shifts and ring closure where the number of σ-bonds increases at the expense of π-bonds without the loss of any fragment and yet result in the formation of desired cyclic product.

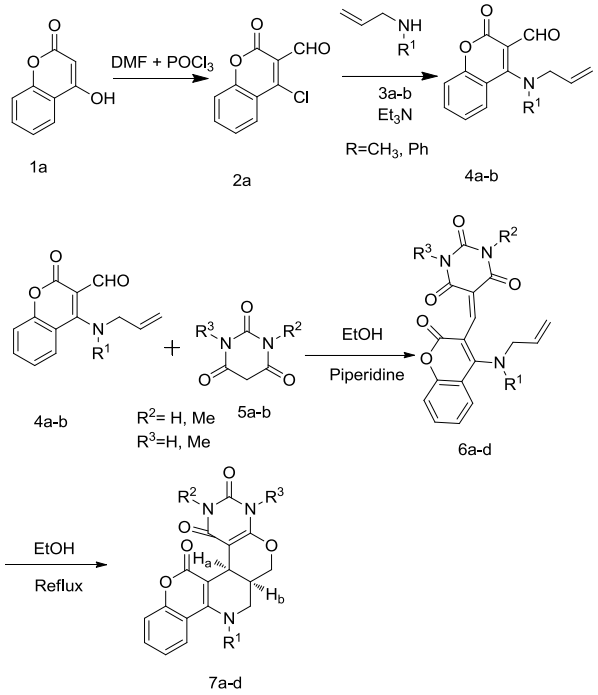
2. Materials and methods:

As a part of continuing efforts towards the synthesis of various heterocyclic compounds, particularly annelated coumarins of biological importance [10], I report here the synthesis of some novel pyrido[2,3-*c*]-coumarin derivatives **7** from the reaction of 4-*N*-pheny/*N*-methyllallylamino-3-formyl coumarins **4** with *N,N*-dimethylmethyl-barbituric acid/ barbituric acid **5** by exploring Diels Alder reaction strategy (**Scheme-1**).

In the reaction protocol, 4-hydroxycoumarins **1** was chosen as the starting material. The key intermediate 4-chloro-3-formylcoumarin **2** was prepared from 4-hydroxycoumarin **1** following the existing reported method [11] with little modification [12]. The reaction of **2** with N-phenylallylamine **3a** in presence of Et_3N using dichloromethane (DCM) as solvent was found to be suitable method to generate 3-formyl-4-*N*-phenylallylaminocoumarin derivative **4a** [13].

The compound **4a** so obtained was reacted with *N*,*N*-dimethylbarbituric acid **5a** in presence of catalytic amount of piperidine in ethanol at room temperature which afforded the Knoevenagel condensed product **6a**. The final cyclization in **6a** was carried out under refluxing condition using ethanol as solvent which gave pyrido[2,3-*c*]coumarin derivative **7a** [14]. The product was obtained in 70% yield after purification. The structure of the compound was ascertained from spectroscopic data. The ^{1}H NMR showed the absence of aldehydic proton and presence of two *N*-Me groups at δ 3.16 and δ 3.28 respectively, which indicates the involvement of *N*,*N*-dimethylbarbituric acid in the reaction process.

3. Results and discussion:



Scheme 1:

The presence of two protons at δ 2.39 as multiplet and one doublet at δ 2.85 evidenced the formation of cyclized product. Moreover, the mass spectra supported the formation of cyclized product by showing the sharp molecular ion peak at 444.2 $(M+H)^+$. The generality of the reaction was established by synthesizing **4a-b**, and utilizing them with *N*,*N*-dimethylbarbituric acid/ barbituric acid in presence of base under thermal condition gave the pyrido[2,3-*c*]coumarin derivatives **7a-d** in good yield. Our observations are depicted in **Table-1**.

Table 1: Synthesis of pyrido[2,3-c]coumarin

Ent.	**R^1**	**R^2**	**R^3**	**Pd.**	**R. T. (h)**
1	Ph	Me	Me	**7a**	2.5
2	Ph	Me	Me	**7b**	3
3	Me	H	H	**7c**	3
4	Me	H	H	**7d**	2.5

Ent. = Entry; Pd. = Product; R. T. = Reaction Time.

4. Conclusions:

In conclusion I have reported the synthesis of some complex pyrido[2,3-*c*]coumarin derivatives from cheap and easily available starting material 4-hydroxycoumarin *via* Diels Alder reaction strategy. The products were isolated simply by filtration almost in pure form.

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[12] **Reprentative procedure for the formation of compound 2:** To a stirred solution of 4-hydroxycoumanin **1a** (6.17 mmol, 1g) in anhydrous DMF (5.2 mL), $POCl_3$ (3.2 mL, 0.02 mmol) was added drop wise at -10 to -5 ^oC. The stirring was continued for 1 h at room temperature and then heated at 60 ^oC for 2 h. The reaction mixture was cooled and then poured into ice under vigorous stirring. On storing the mixture overnight, a pale yellow solid appeared, which was filtered and washed first with 5% Na_2CO_3 solution and then with water. The compound was recrystallized from acetone. The structure of the compound was ascertained as **2a** from spectroscopic data. Compound **2a**: Yield = 61%. mp. 117-118 ^oC (lit m.p. 120-122 °C[23]); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.49 (m, 2H), 7.72-7.78 (m, 1H), 8.13-8.16 (m, 1H), 10.40 (s, 1H). MS (ESI): 209.2 $(M+H)^+$.
[13] To a solution of 4-chloro-3-formyl-coumarin **2a** (419 mg, 2 mmol) in DCM (5 mL), *N*-allylaniline **3a** (266 mg, 2 mmol) and Et_3N (202 mg, 2 mmol) were added. Then, the reaction mixture was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure and the residue washed with petroleum ether. The pure compound **4a** was obtained by column chromatography using 8:2 petroleum ether/ethyl acetate.
Compound **4a**: Yield: 79%; m.p. 85–86°C; ^1H NMR (300 MHz, $CDCl_3$): δ 4.55 (d, J=4.4 Hz, 2H), 5.27 (dd, J=4.2 Hz, 2H), 5.82 (m, 1H), 7.00-7.51 (m, 9H), 10.20 (s, 1H); MS (ESI) 306.3 $(M+H)^+$.
Similarly, compound **4b** is synthesized and characterized.
[14] To an ethanolic solution of 4-N-phenylallylamine-3-formylcoumarin **4a** (1 mmol) in a 100 mL round bottom flask added 1 mmol of active methylene compound **5a** and 1 drop of piperidine and then allowed to stir at room temperature. The reaction mixture becomes yellow within 15 min which shows the formation of the Knoevenagel condensed product. Then the mixture was allowed to reflux for 3–4.5 h. The product **7a** appeared as brownish compound in the reaction mixture. The compound was filtered and recrystallised from 20% $EtOH/CHCl_3$.
Compound **7a**: Yield: 70%; mp. 152-155°C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.20-2.2.20-2.39 (m, 1H, H_b), 2.85 (d, J=4.5 Hz, 1H, H_a), 3.16 (s, 3H, NMe), 3.28 (s, 3H, NMe), 3.42 (d, J=1.5 Hz, 2H, NCH_2), 4.10 (d, J=4.9, 2H, OCH_2), 7.24-7.78 (m, 9H, Ar); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 21.4, 28.2, 29.3, 35.9, 55.2, 65.7, 74.5, 101.2, 114.2, 116.5, 119.3 (2C), 120.3, 122.4, 125.1, 128.7, 129.3 (2C), 142.4, 151.1, 152.3, 154.7, 161.3, 162.5, 163.7; MS (ESI): 444.2 $(M+H)^+$.

Similarly, compound **7b, 7c, 7d** are synthesized and characterized.