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Synthesis of some novel spiro substituted pyrido[2,3-*c*]coumarins by exploring 'tertiary amino effect' reaction strategy

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ABSTRACT

Some novel spiro substituted pyrido[2,3-*c*]coumarin derivatives were synthesized from 4-hydroxycoumarin by exploring 'tertiary amino effect' reaction strategy.

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). Therefore, considerable efforts have been made towards the preparation and synthetic manipulation of pyridocoumarin. But most of these reported methods have many disadvantages like use of organic solvent, costly catalyst etc.[9]

Spiro substituted diverse heterocyclic compounds are available in nature with interesting biological activity.[10] In coumarin, spiro substituted pyranocoumarins are well known and have been extensively studied for their biological activity particularly as antioxidant.[11] However, spiro substituted pyrido coumarin is not reported so far.

α-Cyclization of tertiary amine, which is named as 'tertiary amino effect' by Meth Cohn, is an important reaction strategy that involves 1,5- or 1,6-electrocyclizations to form five or six membered ring systems.[12] These reactions are mechanistically intriguing and synthetically very useful, and thus have been extensively used for the synthesis of various annelated pyridine and pyrrolidine derivatives of biological importance.[13,14] Recently, Ivanov and his co-workers reported an example of α-cyclization of tertiary amines in coumarins by utilizing appropriately substituted coumarin derivatives and acyclic active methylene compounds. The reactions were performed under drastic conditions in acidic medium (refluxing acetic acid) and different types of products were obtained depending on the nature of active methylene compounds.[15]

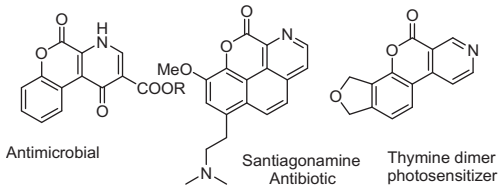

Figure 1. Some biologically important pyrido coumarins.

As a part of our continuing efforts towards the synthesis of various heterocyclic compounds,[16] particularly annelated coumarins of biological importance,[17] we report here the synthesis of some novel functionalized spiro substituted pyrido[2,3-*c*]-coumarin derivatives **7** from the reaction of 4-amino-3-formyl coumarins **4** with *N,N*-dimethylmethyl-barbituric acid/*N*-methylbarbituric acid **5** by exploring 'tertiary amino effect' reaction strategy (Scheme 1). In the reaction protocol, 4-hydroxycoumarins **1** were chosen as the starting material. The key intermediate 4-chloro-3-formylcoumarins **2** were prepared from 4-hydroxycoumarins **1** following the existing reported method[18] with little modification.[19] The reaction of **2a** with diethylamine in the presence of Et_3N using dichloromethane (DCM) as solvent was found to be a suitable method to generate 3-formyl-4-tertiaryamino coumarin derivative **4a**.[20]

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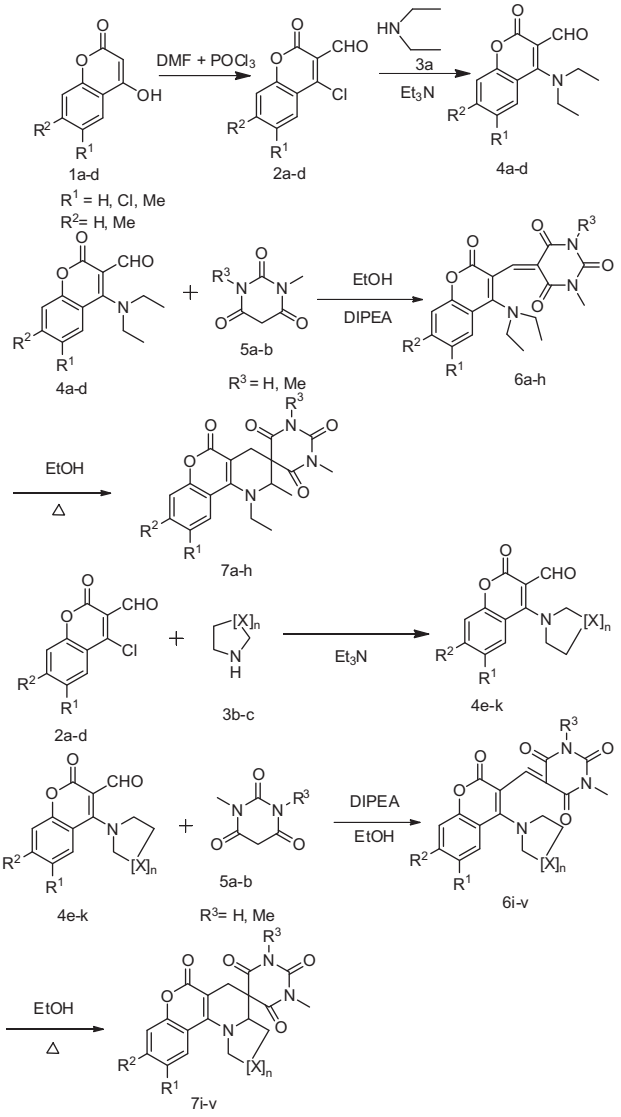
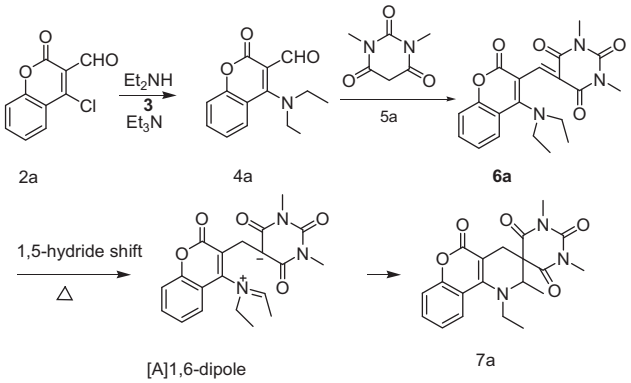


Scheme 1.

Table 1
Synthesis of spiro substituted pyrido[2,3-*c*]coumarin

Ent.	R^1	R^2	$[X]_n$	R^3	Pd.	R.T. (h)
1	H	H	—	Me	**7a**	2.5
2	Cl	H	—	Me	**7b**	3
3	Me	H	—	Me	**7c**	3
4	Me	Me	—	Me	**7d**	2.5
5	H	H	—	H	**7e**	3.5
6	Cl	H	—	H	**7f**	4
7	Me	H	—	H	**7g**	3.5
8	Me	Me	—	H	**7h**	3
9	H	H	$[CH_2)_1$	Me	**7i**	3.5
10	Cl	H	$[CH_2)_1$	Me	**7j**	4.5
11	Me	H	$[CH_2)_1$	Me	**7k**	3.5
12	Me	Me	$[CH_2)_1$	Me	**7l**	3.5
13	H	H	$[CH_2)_1$	H	**7m**	4
14	Cl	H	$[CH_2)_1$	H	**7n**	4.5
15	Me	H	$[CH_2)_1$	H	**7o**	3.5
16	Me	Me	$[CH_2)_1$	H	**7p**	3.5
17	H	H	$[CH_2)_2$	Me	**7q**	4.5
18	Cl	H	$[CH_2)_2$	Me	**7r**	4.5
19	Me	H	$[CH_2)_2$	Me	**7s**	4
20	H	H	$[CH_2)_2$	H	**7t**	5
21	Cl	H	$[CH_2)_2$	H	**7u**	4.5
22	Me	H	$[CH_2)_2$	H	**7v**	4.5

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



Scheme 2.

Compound **4a** so obtained was reacted with *N,N*-dimethylbarbituric acid **5a** in the presence of a catalytic amount of diisopropylethylamine (DIPEA) in ethanol at room temperature which afforded the Knoevenagel condensed product **6a**.[21] The final α-cyclization of tertiary amine in **6a** was carried out under refluxing condition using ethanol as solvent which gave spiro substituted pyrido[2,3-*c*]coumarin derivative **7a**.[22] The product was obtained in 77% yield after purification. The structure of the compound was ascertained from spectroscopic data and elemental analysis. The ^{1}H NMR showed the absence of aldehydic proton and presence of two *N*-Me groups at δ 3.39 and 3.28, respectively, which indicates the involvement of *N,N*-dimethylbarbituric acid in the reaction process. The presence of two isolated protons at δ 2.98 as singlet and one multiplet at δ 3.80 for a single proton evidenced the formation of cyclized product. Moreover, the mass spectra supported the formation of cyclized product by showing the sharp molecular ion peak at 384.5 $(M+H)^+$. The generality of the reaction was established by synthesizing various cyclic and acyclic tertiary amino coumarin derivatives **4a**–**k**, and utilizing them with *N,N*-dimethylbarbituric acid/*N*-methylbarbituric acid in the presence of base to obtain **6**, which under thermal condition gave the spiro substituted pyrido[2,3-*c*]-coumarin derivatives **7a**–**v** in good yield. Our observations are depicted in Table 1.

In our study, it was found that acyclic amino coumarins are more reactive compared to the cyclic amino group, and *N,N*-dimethylbarbituric acid shows better reactivity in comparison with *N*-methyl-barbituric acid.

The possible mechanism which could be accounted for the formation of spiro substituted pyrido[2,3-*c*]coumarin **7a** is shown in Scheme 2. Initial Knoevenagel condensation takes place between compounds **4a** and **5a** which gives an aminodiene system **6a**. The intermediate **6a** under thermal condition undergoes 1,5-hydride shift (sigmatropic shift) to generate 1,6-dipole which subsequently cyclized to give the desired product **7a**.

In summary, we have reported the synthesis of some novel spiro substituted pyrido[2,3-*c*]coumarin derivatives from a cheap and easily available starting material viz 4-hydroxycoumarin by exploring 'tertiary amino effect' reaction strategy. The reaction procedure is mild, work-up procedure is simple and the products were isolated by filtration and washing with ethanol. Further, the reaction protocol can be utilized for the synthesis of many other heterocyclic compounds of importance.

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19. *Representative procedure for the formation of compound* ***2****:* To a stirred solution of 4-hydroxycoumanin **1a** (6.17 mmol, 1 g) in anhydrous DMF (5.2 ml), $POCl_3$ (3.2 ml, 0.02 mmol) was added drop wise at −10 to −5 °C. The stirring was continued for 1 h at room temperature and then heated at 60 °C 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 = 610 mg (61%). mp 117–118 °C (lit mp 120–122 °C[23]); ^{1}H 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 $(M+H)^+$. Similarly, compounds **2b–d** were synthesized and characterized.
20. *Representative procedure for the synthesis of compound* ***4****:* 4-Chloro-3-formylcoumarin **2a** (1 mmol, 208 mg), diethylamine **3a** (1 mmol, 73 mg) and triethylamine (1 mmol, 101 mg) in 5 ml DCM were taken in a round bottomed flask and stirred at room temperature for 3 h. After completion of the reaction (as indicated by TLC), the solution was poured in water, and extracted with DCM. The solvent was evaporated and the residue was purified by column chromatography on silica gel using 8:2 hexane and ethyl acetate as eluent. The structure of the isolated compound was ascertained as **4a** from spectroscopic data and elemental analysis. Yield: 190 mg (78%); *Compound* ***4a****:* Brown solid; mp 181 °C. IR ($CHCl_3$): ν_{max} 1635, 1719, 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.07 (s, 1H), 7.53 (m, 4H), 3.73 (m, 4H), 1.35 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.8 (2C), 45.6 (2C), 107.8, 122.3, 124.4, 125.6, 125.8, 128.7, 156.7, 167.8, 187.7, 193.5; MS (ESI): 246.3 $(M+H)^+$; Anal. Calcd for $C_{14}H_{16}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.34; H, 6.09; N, 5.64. Similarly, other compounds **4b–k** were synthesized and characterized.
21. *Representative procedure for the synthesis of compound* ***6****:* A mixture of compound **4a** (1 mmol, 245 mg) and **5a** (1 mmol, 156 mg) was taken in a round bottomed flask containing ethanol (5 ml). To this, catalytic amount of diisopropylethylamine (DIPEA) was added and the reaction mixture was stirred at room temperature for 1 h. The solid formed in the reaction process was filtered and purified by washing with ethanol and dried. The structure of the compound was ascertained as **6a** from spectroscopic data. Yield: 270 mg (70%); *Compound* ***6a****:* Light yellow; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.79 (s, 1H), 7.47 (m, 4H), 3.73 (m, 4H), 3.39 (s, 3H), 3.28 (s, 3H), 1.35 (m, 6H). Similarly, other compounds **6b–v** were synthesized and characterized.
22. *Representative procedure for the synthesis of compound* ***7****:* Compound **6a** (2 mmol, 766 mg) was refluxed in ethanol (5 ml) for 2.5 h. After completion of the reaction (as indicated by TLC), the reaction mixture was cooled to room temperature and the solid formed was filtered. Finally the product was purified by recrystallization from ethanol. The structure of the compound was ascertained as **7a** from spectroscopic data and elemental analysis. Yield: 77% (295 mg); *Compound* ***7a****:* Yellow solid; mp 258.6–259.3 °C. IR ($CHCl_3$): ν_{max} 1606.4, 1685.1, 1749.0, 2878.1 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21–7.51 (m, 4H), 3.80 (m, 1H), 3.39 (s, 3H), 3.28 (s, 3H), 2.98 (s, 2H), 2.67 (m, 2H), 1.46 (t, 3H), 1.12 (d, J = 6.81 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.92, 17.65, 22.27, 28.79, 29.75, 49.04, 51.85, 103.48, 116.41, 117.86, 123.34, 123.64, 130.57, 149.32, 151.34, 152.77, 161.85, 168.51, 169.42; MS (ESI): 384.5 $(M+H)^+$; Anal. Calcd for $C_{20}H_{22}N_3O_5$: C, 62.65; H, 5.52; N, 10.96. Found: C, 62.33; H, 5.45; N, 10.41. Similarly, compounds **7b–v** were synthesized and characterized.
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