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Highly efficient and regioselective synthesis of keto-enamine Schiff bases of 7-hydroxy-4-methyl-2-oxo-2*H*-benzo[*h*]chromene-8,10-dicarbaldehyde and 1-hydroxynaphthalene-2,4-dicarbaldehyde☆

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Abstract—A series of novel Schiff bases has been synthesized by reacting 7-hydroxy-4-methyl-2-oxo-2*H*-benzo[*h*]chromene-8,10-dicarbaldehyde **3** and 1-hydroxynaphthalene-2,4-dicarbaldehyde **8** with several primary alkylamines in ethyl alcohol at room temperature within 1–2 min. Schiff bases **4a**–**i** and **9** were formed regioselectively by condensation with only one aldehyde, which is in chelation with a hydroxyl group. Extensive 2D NMR spectroscopic studies revealed that all the compounds **4a**–**i** and **9** exist in the keto-enamine tautomeric form at room temperature. The high reactivity, regioselectivity and stable keto-enamine tautomeric form are due to the presence of an electron-withdrawing aldehyde group.

Coumarins are widely available from the natural sources[1] and exhibit various biological activities such as anticancer,[2] inhibition of platelet aggregation,[3] inhibition of steroid 5α-reductase[4] and anti HIV activity.[5] In continuation of our drug discovery programme to synthesize biologically active compounds, we wanted to prepare 4-substituted coumarin derivatives. Our synthetic strategy began with the widely used Pechmann reaction[6] between naphthalene-1,5-diol **1** and a β-keto-ester to give 7-hydroxy-4-methyl-benzo[*h*]chromen-2-one **2**. Coumarin **2** was subjected to a Duff reaction[7] to give 7-hydroxy-4-methyl-2-oxo-2*H*-benzo[*h*]chromene-8,10-dicarbaldehyde **3**. We further wanted to introduce a nitrogenous side-chain to improve the pharmacological activity. Dialdehyde **3** was condensed with various primary amines[8] to give the respective Schiff base imines. The ^{1}H spectra of these compounds seemed to be consistent with the expected enol-imine structure **6**, however in the ^{13}C NMR spectra, we found unexpected signals. A careful examination by the 2D NMR spectroscopic experiments such as HSQC and HMBC revealed that all these compounds (**4a**–**i** and **9**) were present in the keto-enamine form at room temperature.

In this Letter, we describe the characterization of the Schiff base keto-enamines using extensive 2D NMR spectral data, factors involved in the stability of enamines, the rapidity of the reaction and regioselective Schiff base formation. A comparable tautomeric phenomenon has recently been discovered during the synthesis of Schiff bases of the naturally occurring biologically active yellow pigment, gossypol, which was isolated from cotton plants.[9] For Schiff bases of simple aldehydes such as salicylaldehyde, the enol-imine form was the only observed form;[10] however, most of the Schiff bases show tautomerism (imine–enamine). Recently, Amanda et al. synthesized macrocyclic compounds by incorporating 1,4-diformyl-2,3-dihydroxynaphthalene and obtained macrocyclic Schiff bases as a mixture of tautomers.[11]

7-Hydroxy-4-methyl-2-oxo-2*H*-benzo[*h*]chromene-8,10-dicarbaldehyde **3** was condensed with *n*-butylamine to obtain Schiff base **5**. The ESI-Mass spectrum gave a molecular ion at *m*/*z* 338 indicated the formation of the required product. Since the hydrogen of the formyl group, which was present at C-8, chelated with adjacent hydroxyl group (C-7), we anticipated that the Schiff base

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formation, which is present in the enol-imine form **6**. The ^{1}H NMR spectrum of the product (Fig. 1) shows signals at δ 11.1 and 13.5 and we assumed the former belongs to the proton of the formyl group (C-8) and the latter to a chelated hydroxyl group (C-7). The ^{13}C NMR spectrum (Fig. 1) shows two unexpected signals at δ 179.1 (CO) and 164.0 (CH) and led us to speculate that the product had a keto-enamine form. In addition, in the ^{1}H spectrum there was a doublet at δ 8.02, which was in a one bond correlation with the signal at δ 164.0 in the HSQC spectrum. In the ^{1}H–^{1}H COSY spectrum, the chelated proton (δ 13.5) gave correlations with the protons present at δ 8.02 and δ 3.68; this was only possible if the product existed as keto-enamine **4** (Scheme 1). In the keto-enamine form, the NH proton would be chelated with carbonyl at C-7 and as a result would give correlations with the enamine proton (δ 8.02, doublet) and methylene (N–CH_2, multiplet) in the COSY spectrum. In the HMBC spectrum, the enamine proton (δ 8.02) gave long-range correlations with signals at δ 179.1 (CO), 108.7 (C-8), 136.9 (C-9) and 51.0 (N–CH_2), which support the existence of the keto-enamine form. The HMBC correlation (Fig. 2) of the formyl proton (δ 11.1) with δ 136.9 (C-9) and 120.9 (C-11) supported the presence of the second formyl group, located at C-10. The final analysis with all the spectral data led to the keto-enamine structure as **4e**, not **5** or **6**.

We prepared the diformyl derivative **8** of α-naphthol **7** using the Duff reaction and subsequently reacted **8** with *n*-butylamine (Scheme 2). We again observed regioselective Schiff base formation **9**, present in the keto-enamine form,[12] but not enol-enamine **10** or **11**. Even at reflux temperature, only one product **9** was formed and the formyl group present on C-4 remained intact.

Amanda et al.[11] have observed similar keto-enamine products along with enol-enamine products from 1,4-diformyl-2,3-dihydroxynaphthalene, in which both formyl groups are *para* to each other, hence a mixture of products (enol-enamine and keto-enamine) was formed at 80 °C, over a longer reaction time (12 h) with low yields (46%). Similarly, Przybylski et al.[9] synthesized

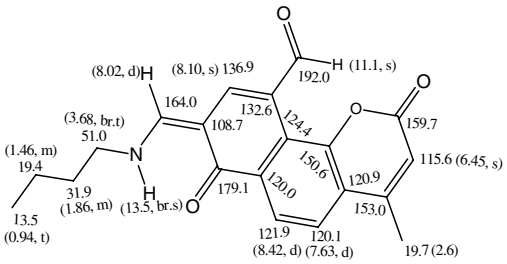


Figure 1. ^{1}H NMR (values in parentheses) and ^{13}C NMR spectral data of compound **4e** in $CDCl_3$.

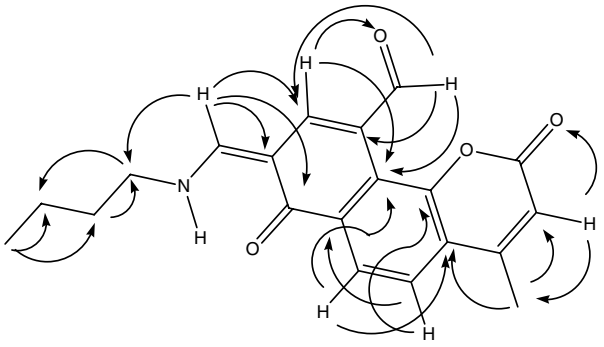
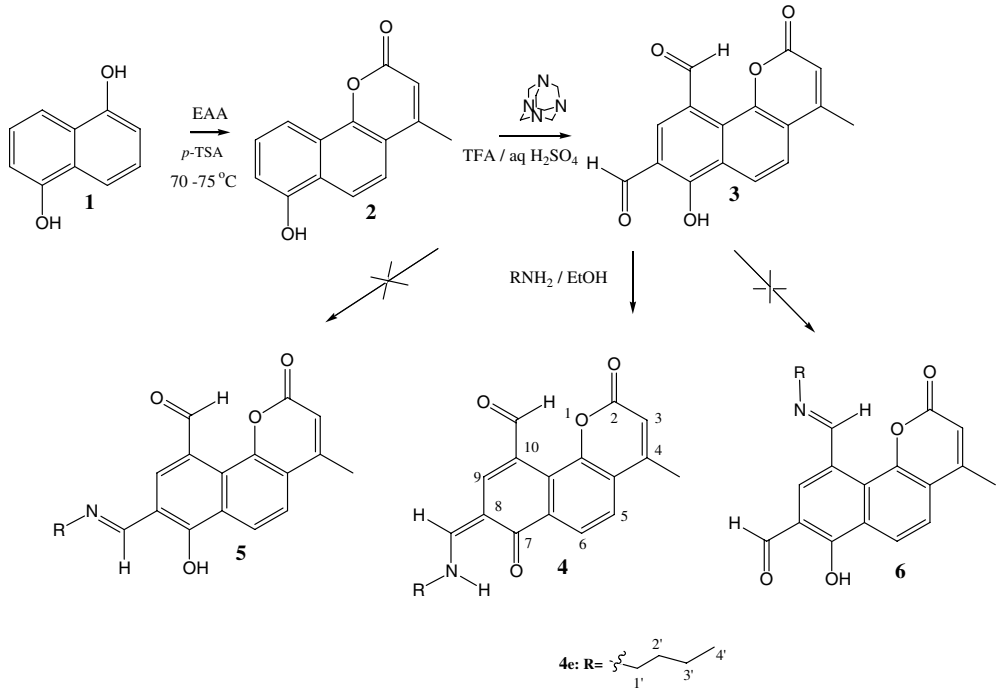
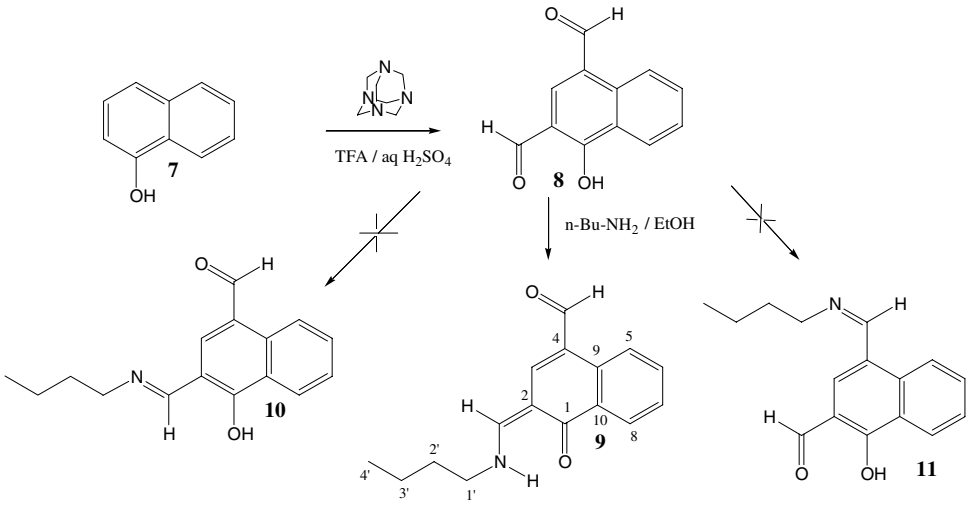


Figure 2. Selected ^{1}H to ^{13}C-HMBC correlations of compound **4e** in $CDCl_3$.



Scheme 1. Synthesis of 7-hydroxy-4-methyl-2-oxo-2*H*-benzo[*h*]chromene-8,10-dicarbaldehyde Schiff bases **4a**–**i**.



Scheme 2. Synthesis of 1-hydroxynaphthalene-2,4-dicarbaldehyde Schiff bases.

gossypol Schiff bases using reflux for 3 h (yield: 71%). Gossypol contains an electron releasing hydroxyl group, which is *meta* to the formyl groups here, the inductive effect of the hydroxyl group might be dominating, to stabilize the keto-enamine form. Other groups[13] have synthesized Schiff bases under drastic conditions of high temperature, long reaction times, with catalysts and in low yields. In contrast to this, our Schiff base preparations took only 1–2 min, without any catalyst, at room temperature with yields ranging from 80% to 92%. This may be attributable to the presence of the electron-withdrawing formyl group at the *meta* position (see Table 1).

In summary, we have synthesized several Schiff bases of 7-hydroxy-4-methyl-2-oxo-2*H*-benzo[*h*]chromene-8,10-dicarbaldehyde and 1-hydroxynaphthalene-2,4-dicarbaldehyde in high yields, regioselectively and within a short time at room temperature without any catalyst. Our results show that the formation of extended conjugated stabilized keto-enamines is a sufficient driving force to overcome the aromatic stabilization of the second ring in the naphthalene. In addition to this, the presence of electron-withdrawing groups at the *meta* position to *ortho* hydroxy formyl group accelerate the reaction rate. We are the first group to observe the regioselective Schiff base formation in a coumarin nucleus, which is present in the keto-enamine form. Since these coumarin derivatives are highly fluorescent, the utility of these compounds to act as novel angiogenesis inhibitors with high selectivity over tumor cells is under investigation as it is potentially possible to inhibit and detect tumor angiogenesis simultaneously.

Table 1. Keto-enamine tautomeric Schiff bases (**4a**–**i** and **9**) of 7-hydroxy-4-methyl-2-oxo-2*H*-benzo[*h*]chromene-8,10-dicarbaldehyde **3** and 1-hydroxynaphthalene-2,4-dicarbaldehyde **8**

Entry	R	Time (s)	Isolated yields (%)	Mp (°C)
4a	Methyl	45	88	>290
4b	Ethyl	55	90	242
4c	Propyl	40	92	222
4d	Isopropyl	25	85	240
4e	*n*-Butyl	60	83	268
4f	*t*-Butyl	50	90	>290
4g	*n*-Heptyl	65	80	215
4h	2-Morpholino ethyl	75	80	195
4i	3-Morpholino propyl	60	85	172
9	*n*-Butyl	55	80	95

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Supplementary data

Spectral data of all the compounds associated with this article will be available as supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.044.

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12. 300 MHz ^{1}H NMR spectral data of compound **9** in $CDCl_3$: δ 0.96–1.00 (3H, t, $J = 6.0$ Hz, H-4′), 1.46–1.49 (2H, m, H-3′), 1.71–1.80 (2H, m, H-2′), 3.58–3.59 (2H, br m, H-1′), 7.49 (1H, ddd, $J = 9.0$ Hz, 6.0 Hz, 3.0 Hz), 7.51 (1H, s, H-3), 7.70 (1H, ddd $J = 9.0$ Hz, 6.0 Hz, 3.0 Hz), 7.83 (1H, d, $J = 9.0$ Hz, CH=N), 8.47 (1H, dd, $J = 6.0$ Hz, 3.0 Hz), 9.18 (1H, d $J = 9.0$ Hz), 9.87 (1H, CHO), 13.1 (1H, br s, NH); 75 MHz ^{13}C NMR: δ 12.2 (C-4′), 18.4 (C-3′), 30.7 (C-2′), 49.4 (C-1′), 106.7 (C-2), 118.9 (C), 123.9 (CH), 124.4 (CH), 124.9 (CH), 129.2 (C), 130.8 (CH), 132.7 (C), 145.1 (C-3), 161.1 (C=N), 180.0 (C-1), 189.3 (CHO); ESI-Mass: 256 (M+1).
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