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UNUSUAL REACTION OF 6-FORMYL-2-OXO-2H-BENZO[h]CHROMENE-3-CARBOXYLIC ACID ETHYL ESTER WITH ALIPHATIC AMINES

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The unusual reaction of coumarone systems when exposed to aliphatic amines is described. The stability and formation of these compounds is discussed with respect to its substituents at para position, and it was found that the para substituents have no role to play.

Keywords: 1-Hydroxynaphthalene-2,4-dicarbaldehyde; keto-enamine; NMR spectroscopy; regioselectivity; Schiff bases

INTRODUCTION

Coumarins and their derivatives have attracted considerable attention from organic and medicinal chemists for many years because a large number of natural products contain this heterocyclic nucleus,[1] and they exhibit various biological activities such as anticancer activity,[2] inhibition of platelet aggregation,[3] inhibition of steroid 5α-reductase,[4] and anti-HIV activity.[5] In continuation of our drug discovery program, we have reported the synthesis and potential antidyslipidemic and antioxidant activity of novel Schiff bases from 7-hydroxy-4-methyl-2-oxo-2H-benzo[h]chromene-8,10 dicarbaldehyde in which the reactions were regioselective and products were in the keto-enamine form, in which the aromaticity of the relevant ring was disrupted.[6,7] Further, our efforts to bring the free aldehyde at position 4 into reaction failed both with increasing molar ratio of the alkyl amine and also by increasing the reaction temperature to reflux, and we rather discovered vicarious nucleophilic substitution in enamine derivatives of 1-hydroxynaphthalene-2,4-dicarbaldehyde.[8]

To prepare a variety of coumarin derivatives and their Schiff bases, we embarked upon synthesis of coumarins from 1-hydroxynaphthalene-2,4-dicarbaldehyde **1**, which in turn was obtained from Duff reaction of α-naphthol (Scheme 1). Our synthetic strategy began with the widely used Knoevenagel

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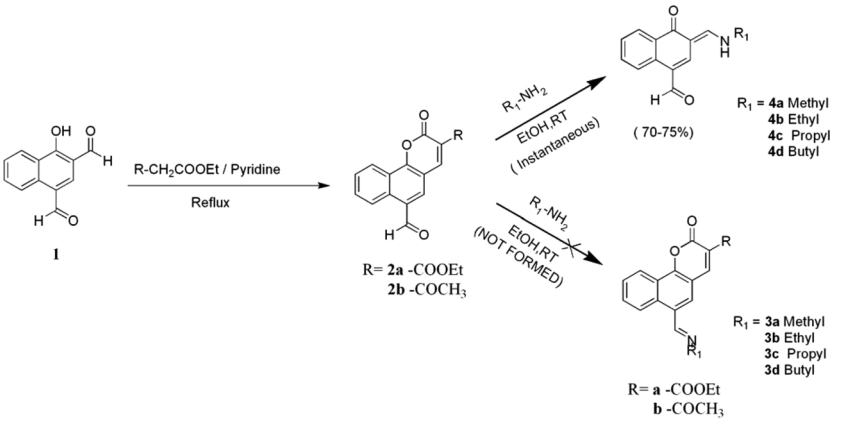


Scheme 1. Synthesis of **2a,b** and conversion to **4a–d**.

reaction[9] between **1** and a diketoester to give 3-acetyl-2-oxo-2H-benzo [h]chromene-6-carbaldehyde **2a**. The product formed was unambiguously characterized by spectroscopic studies including 2D NMR [correlation spectroscopy (COSY), heteronuclear multiple quantum correlation (HMBC), and heteronuclear single quantum correlation (HSQC)] (Fig. 1). We tried to introduce the nitrogenous side chain to product **2a** (which has a free aldehyde) to improve its pharmacological activity. The results of investigations form the subject matter of this letter.

RESULTS AND DISCUSSION

When treated with aliphatic amines under ethanolic conditions, compounds **2a** and **2b** furnished compounds within a short time, which we thought to be **3a**–**d**.

Electrospray ionization–mass spectrometry (ESI-MS) of the product gave a molecular ion at m/z 214. The ^{1}H NMR of the product in addition to other signals showed a signal at δ 9.77 for a free aldehyde, and the product existed in the keto-enamine form as the NH proton gave a cross peak with enamine proton at δ 8.45 in the COSY spectrum. In ^{13}C NMR, there was no peak corresponding to lactone moity at δ 155.6 ppm. The final analysis with all the spectral data led to the discovery that the compound **2a** was converted to **4a** on addition of a methylamine. It is interesting to note the same product was also formed directly from 1-hydroxy naphthalene-2,4-dicarbaldehyde **1** on treatment with methyl amine.[8]

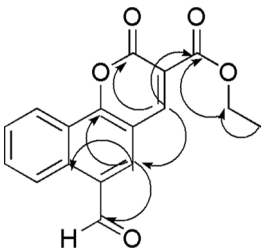


Figure 1. Selected HMBC corelations of compound **2a** in $CDCl_3$.

Though efforts are ongoing in our laboratory to delineate the mechanism of this reaction, the most plausible mechanism seems to be a ring opening (by transesterification/solvent assisted) and retro-Knoevenagel condensation,[10] resulting in the regeneration of the aromatic dicarbaldehyde (starting material) and then its subsequent reaction with the amine present, giving rise to enamine product. Overall, we believe, it is a stepwise process with participation of protic solvent (ethanol).

These perplexing results forced us to delineate the role of electron-withdrawing *para* aldehyde in compound **1**. We thought the electron-withdrawing aldehyde group at the *para* position was responsible for this existence in keto-enamine form and its unusual stability.

It is worth mentioning that the aldehyde at position 2 that was in chelation (hydrogen bonded) with OH was more reactive and in NMR resonated at δ 10.25 compared with the aldehyde at position 4, which in turn resonated at δ 9.98. Hence, the addition of either alkyl or aromatic amine instantaneously resulted in the enamine derivatives, leaving the free aldehyde at position 4.

Recently, Blanco and Ferretti[11] have studied the solvent and substituent effects on the conformational equilbria and intramolecular hydrogen bonding of 4-substituted-2-hydroxybenzaldehydes. The key findings of this study were that the electron-withdrawing groups, by decreasing the $O_{11}H_{13}O_{12}$ H-bond angle, increase the corresponding O_{11}–H_{13} interaction distance and consequently the strength of the intramolecular hydrogen bonding decreases (Fig. 2).

Hence, in the 1-hydroxynaphthalene-2,4-dicarbaldehyde **1** system, we thought because of the electron-withdrawing group at position 4 the molecule occurs in the least stable conformer (i.e., open *cis* conformer rather than stable closed *cis* conformer or *trans* conformer) (Fig. 2). This could explain the high reactivity of this system, containing a reactive electrophilic aldehyde group at position 2.

To our surprise, when 1-hydroxy-4-methyl-naphthalene-2-carbaldehyde **6** (isolated and characterized as a minor side product of the Duff reaction) was treated with n-butyl amine and also with p-toluidine, it instantaneously resulted in the respective keto-enamine products **7b** and **7c** (Scheme 2). These results indicate that Schiff bases derived from ortho-hydroxy benzaldehyde group in naphthalene-based system invariable exist in keto-enamine regardless of the nature of the substituent at the *para*-position.

Robert et al. have synthesized highly stable 3-carbaxamide coumarins from 3-carbaxylic ester coumarins.[9] To the best of our knowledge, this is the first example

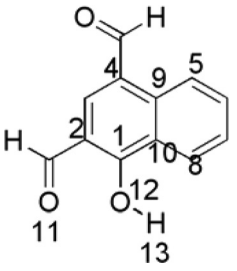
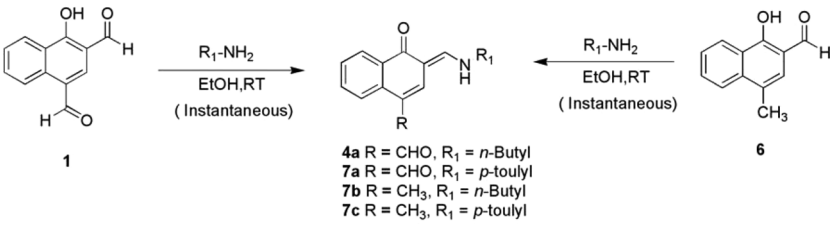


Figure 2. Open *cis* conformation of 1-hydroxynaphthalene-2,4-dicarbaldehyde.



Scheme 2. Synthesis of keto-enamine **4a**, **7a–c**.

of rearrangement of stable benzocoumarin with an alkyl amine. The benzocoumarins (**2a** and **2b**) underwent reaction not only with methylamine but also with ethyl, propyl, and butyl amine; the reaction times and yields were comparable with those of reaction products of methyl amine. All the reactions were rapid, and almost 70–75% of the reactant underwent reaction to the corresponding keto-enamine.

Finally, the exceptional stability of the final keto-enamine product deserves some comments. The extra stabilization due to extended conjugation in these systems helps to overcome the aromatic stabilization. There are two reasons that contribute to the additional stability. First, the carbon–carbon single bond between the two double bonds in a conjugated diene is derived from the overlap of two carbon sp^2 orbitals (i.e., it is in fact an sp^2–sp^2 single bond and hence stronger). Second, there is the overlap of 2p orbitals across the carbon–carbon bond, connecting the two-alkene units. That is, л bonding not only occurs within each of the alkene units but between them as well. Thus, the 2p orbitals on the central carbon are in the parallel alignment necessary for overlap. The additional bonding associated with this overlap provides additional stability to the molecule.

CONCLUSIONS

In conclusion, we are the first group to discover this unusual reaction in benzocoumarin derivatives. Also, the role of *para* substituent (both electron withdrawing and releasing) in the ortho-hydroxy benzaldehyde group in naphthalene-based system seems to have no effect on the final outcome of its reaction with primary amines.

EXPERIMENTAL

Melting points were recorded on a Buchi-530 capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were run on Bruker Avance DPX 300-MHz spectrometer in $CDCl_3$ (δ 7.28) or DMSO-d_6 (2.50), and tetramethylsilane (TMS) was used as internal standard. Data reported are as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) in Hertz, integration assignment]. ESI mass spectra were recorded on a Jeol S × 102/DA-6000. Silica gel (60–120 mesh) was used as stationary phase to isolate the compounds.

Synthesis of 6-Formyl-2-oxo-2H-benzo[h]chromene-3-carboxylic Acid Ethyl Ester (2a)

Pyridine (15 ml) was added to an equivalent mixture of 1-hydroxy naphthalene-2,4-dicarbaldehyde **1** (2 g, 10 mmol) and diethyl malonate (2.4 g, 15 mmol). The mixture was vigorously refluxed for 12 h. After completion of the reaction, it was neutralized with aq. HCl and extracted with $CHCl_3$ (3×50 ml). $CHCl_3$ extract was dried over anhy. Na_2SO_4 and concentrated in a strong vacuum. The crude product thus obtained was purified by column chromatography (60–120) to furnish 1.63 g (55% yield) of pure benzocoumarin **2a** as a white solid.

6-Formyl-2-oxo-2H-benzo[h]chromene-3-carboxylic Acid Ethyl Ester (2a)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.36 (s, 1H), 9.30 (d, $J = 8.6$ Hz, 1H), 8.73 (s, 1H), 8.64 (d, $J = 7.8$ Hz, 1H), 8.08 (s, 1H), 7.89 (t, $J = 7.0$, 1H), 7.78 (t, $J = 7.8$ Hz, Hz, 1H), 4.46 (q, $J = 7.2$ Hz, 2H), 1.45 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.08, 161.42, 155.74, 154.43, 147.36, 134.42, 131.61, 131.31, 127.41, 127.28, 124.05, 122.28, 121.72, 116.75, 111.12, 61.14, 12.94; ESI (m/z) 297 $[M + H]^+$; ; IR (KBr, cm^{-1}): 3433, 2980, 2875, 1622, 1610; yield: 55%; solid; mp 199°C.

3-Acetyl-2-oxo-2H-benzo[h]chromene-6-carbaldehyde (2b)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.39 (s, 1H), 9.32 (d, $J = 8.9$ Hz, 1H), 8.71(s, 1H), 8.65 (d, $J = 7.9$ Hz, 1H), 8.10 (s, 1H), 7.90 (t, $J = 7.9$, 1H), 7.79 (t, $J = 7.4$ Hz, 1H), 2.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 199.53, 197.13, 163.35, 161.85, 152.95, 142.51, 137.81, 137.57, 133.73, 133.63, 130.56, 129.18, 128.44, 127.89, 118.32, 35.52; ESI (m/z) 267 $[M + H]^+$; IR (KBr, cm^{-1}): 3435, 2984, 2865, 1625, 1605; yield: 50%; solid; mp 208°C.

Synthesis of 3-Methylaminomethylene-4-oxo-3,4-dihydro-naphthalene-1-carbaldehyde (4a)

Absolute ethanol (5 ml) was added to the benzocoumarin **2a** (0.2 g, 0.67 mmol) and methylamine (0.041 g, 1.34 mmol) and stirred at room temperature for 1 to 2 min. After completion of the reaction, ethanol was removed tin a strong vacuum, and the mixture was filtered and washed with water. The crude product was purified by column chromatography over silica (60–120) to provide pure enamine **4a** as yellow solid.

3-Methylaminomethylene-4-oxo-3,4-dihydro-naphthalene-1-carbaldehyde (4a)

^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.43 (s, 1H), 9.77, (s, 1H), 9.11 (d, J =8.2 Hz, 1H), 8.45 (d, $J = 13.8$ Hz, 1H), 8.32 (d, $J = 8.8$ Hz, 1H), 7.85 (s, 1H), 7.7–7.65 (m, 1H), 7.5–7.45 (m, 1H), 3.39 (s, 1H); ESI (m/z) 214 $[M + H]^+$; IR (KBr cm^{-1}): 3444, 2938, 1633, 1596, 1351; yield: 75%; solid; mp 213°C.

3-Ethylaminomethylene-4-oxo-3,4-dihydro-naphthalene-1-carbaldehyde (4b)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.22 (s, 1H), 9.88 (s, 1H), 9.2 (d, $J = 12.4$ Hz, 1H), 8.49 (d, $J = 9.1$ Hz, 1H), 7.9 (d, $J = 12.5$ Hz, 1H), 7.74–7.68 (m, 1H), 7.54–7.5 (m, 2H), 3.73–3.64 (m, 2H), 1.48 (t, $J = 7.2$ Hz, 3H); ESI (m/z) 228 $[M + H]^+$; IR (KBr cm^{-1}): 3442, 2941, 1632, 1595, 1350; yield: 72%; solid; mp 225°C.

3-Butylaminomethylene-4-oxo-3,4-dihydro-naphthalene-1-carbaldehyde (4c)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.14 (s, 1H), 9.85 (s, 1H), 9.17 (d, $J = 8.2$ Hz, 1H), 8.46 (d, $J = 8.3$ Hz, 1H), 7.82 (d, $J = 9.9$ Hz, 1H), 7.68 (t, $J = 9.2$ Hz, 1H), 7.52–7.46 (m, 2H), 3.57 (m, 2H), 1.78–1.70 (m, 2H), 1.52–1.43 (m, 2H), 0.99 (t, $J = 7.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.39, 180.09, 161.1, 145.11, 132.79, 130.82, 129.2, 124.92, 124.45, 123.99, 118.96, 106.71, 49.41, 30.76, 18.44, 12.22; ESI (m/z) 256 $[M + H]^+$; IR (KBr cm^{-1}): 3426, 2925, 2845, 1628, 1594, 1352; Yield: 74%; solid; mp 95°C.

3-Heptylaminomethylene-4-oxo-3,4-dihydro-naphthalene-1-carbaldehyde (4d)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.17 (s, 1H), 9.87 (s, 1H), 9.19 (d, $J = 8.2$ Hz, 1H), 8.48–8.45, (m, 1H), 7.9 (d, $J = 12.8$, 1H), 7.69 (m, 1H), 7.54–7.48 (m, 2H), 3.67–3.58 (m, 2H), 1.46–1.22 (m, 10H), 0.89 (t, $J = 6.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.42, 180.12, 159.46, 145.13, 132.8, 130.84, 129.23, 125.02, 124.41, 124.06, 119.04, 106.54, 56.37, 36.09, 30.25, 24.4, 21.18, 20.11, 12.71; ESI (m/z) 298 $[M + H]^+$; IR (KBr, cm^{-1}): 3429, 2923, 2860, 1632, 1595, 1352; yield: 70%; liquid.

1-Hydroxy-4-methyl-naphthalene-2-carbaldehyde (6)

^{1}H NMR ($CDCl_3$, 200 MHz) δ 12.33 (s, 1H), 9.68 (s, 1H), 8.28 (d, $J = 9.8$ Hz, 1H), 7.7 (d, $J = 8.5$ Hz, 1H), 7.52 (t, $J = 8.5$ Hz, 1H), 7.38 (t, $J = 7.3$ Hz, 1H), 7.0 (s, 1H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 194.93, 159.20, 135.45, 129.16, 124.59, 124.41, 124.01, 123.45, 123.27, 122.81, 112.41, 12.98; ESI (m/z) 186 $[M + H]^+$; IR (KBr, cm^{-1}): 3432, 2980, 2865, 1625, 1593, 1350; yield: 10%; solid; mp 69°C.

4-Oxo-3-(p-tolylamino-methylene)-3,4-dihydro-naphthalene-1-carbaldehyde (7a)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 15.11 (s, 1H), 9.98 (s, 1H), 9.2 (d, $J = 8.04$ Hz, 1H), 8.51 (d, $J = 8.3$ Hz, 1H), 8.38 (d, $J = 10.9$ Hz, 1H), 7.76–7.71 (m, 1H), 7.64 (s, 1H), 7.58–7.53 (m, 1H), 7.3–7.27 (m, 4H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.65, 179.61, 152.95, 144.42, 136.42, 134.8, 132.61, 131.23, 129.45, 128.68, 125.35, 124.54, 124.18, 120.59, 117.38, 107.92, 19.8; ESI (m/z) 290 $[M + H]^+$; ; IR (KBr cm^{-1}): 3416, 2922, 2815, 1595, 1443, 1353; yield: 95%; solid; mp 186°C.

2-Butylaminomethylene-4-methyl-2H-naphthalen-1-one (7b)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.28 (s, 1H), 8.50 (d, $J = 7.9$ Hz, 1H), 7.71–7.41 (m, 3H), 7.44 (t, $J = 7.8$ Hz, 1H), 6.71 (s, 1H) 3.46 (t, $J = 6.7$ Hz, 2H), 2.4 (s, 3H), 1.72–1.62 (m, 2H), 1.49–1.33 (m, 2H) 0.97–0.88 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.80, 159.14, 136.10, 129.09, 128.95, 125.80, 124.63, 123.54, 122.70, 118.01, 106.96, 49.67, 31.32, 18.55, 17.46, 12.34; ESI (m/z) 242 $[M + H]^+$; IR (KBr, cm^{-1}): 3425, 2945, 2875, 1630, 1593; yield: 98%; liquid.

4-Methyl-2-(p-tolylamino-methylene)-2H-naphthalen-1-one (7c)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 14.73 (s, 1H), 8.49 (d, $J = 7.3$, 1H), 8.23 (s, 1H), 7.74 (d, $J = 7.6$ Hz, 1H), 7.6 (t, $J = 6.3$ Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 1H), 7.22–7.16 (m, 4H), 6.86 (s, 1H), 2.44 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.36, 155.14, 140.84, 137.07, 136.40, 130.68, 130.53, 129.01, 127.21, 125.82, 125.6, 124.45, 122.52, 119.46, 115.72, 110.84, 21.40, 19.2; ESI (m/z) 276 $[M + H]^+$; IR (KBr, cm^{-1}): 3442, 2933, 1622, 1590, 1350; yield: 95%; solid; mp 84°C.

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