# Synthesis of 6,8-diarylimino-7*H*-pyrano[3,2-*c*:5,6-*c′*]dicoumarins; chemoselective hydrolysis of the ether- and imino-functions

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$POCl_3$-induced dehydration of 3,3′-methylenedi(2-arylamino-4*H*-chromen-4-ones) gives 6,8-diarylimino-7*H*-pyrano[3,2-*c*:5,6-*c′*]dicoumarins, which undergo chemoselective hydrolysis of the imino function to form 7*H*-pyrano[3,2-*c*:5,6-*c′*]dicoumarins by heating with HCl in methanol However, cleavage of the ether function occurs upon heating in acetic acid to give 3,3′-methylenedi(2-arylamino-4*H*-chromen-4-ones).

**Keywords:** 2-aminochromone-3-carbaldehyde, coumarin, iminocoumarin, bischromone, 1-benzopyran, phosphorous oxychloride

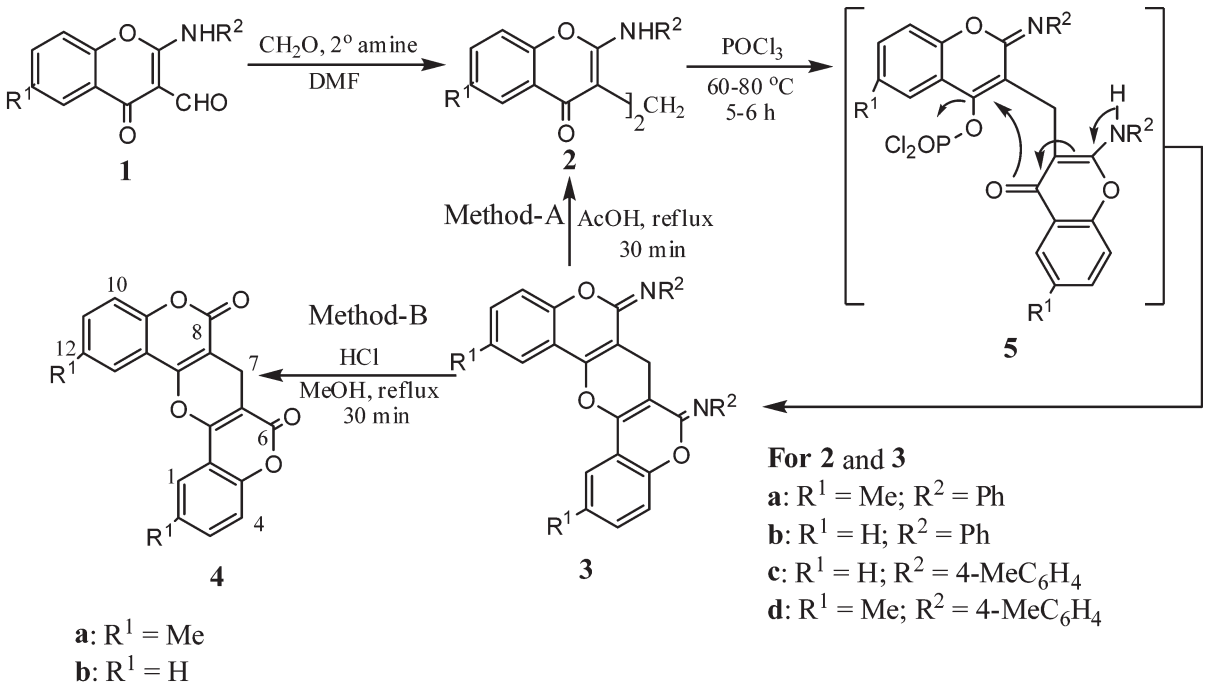
Iminocoumarins are an important class of compounds for a variety of applications. Besides their antimicrobial activity,[1] some iminocoumarin dyes act as photosensitisers for dye-sensitised solar cells.[2] Iminocoumarin-based zinc-sensors have been developed, which are suitable for ratiometric fluorescence imaging of neuronal zinc.[3] Recently, iminocoumarin-based fluorescent probes have been developed for the selective detection of dual specific protein-tyrosine phosphatases.[4]

Although derivatives of 3,3′-methylene-di(4-hydroxycoumarin) (commonly known as dicoumarols) have been synthesised readily from 4-hydroxycoumarin and an appropriate aldehyde under various conditions,[5] the corresponding diiminocoumarins are scarce in the literature. Iminocoumarins are generally synthesised from salicylaldehyde by the action of cyanoacetamide,[1] malononitrile or ethyl cyanoacetate.[6] They have also been obtained by a Cu-catalysed multicomponent reaction of *o*-hydroxyacetophenone, an appropriate alkyne and an alkanesulfonyl azide.[7]

In continuation of our studies on the deformylative Mannich reaction on chromone-3-carbaldehyde,[8] we have reported[9] the synthesis of 3,3′-methylenedi(2-arylamino-4*H*-chromen-4-ones) **2** by heating 2-arylaminochromone-3-carbaldehydes **1** with secondary amines such as sarcosine, piperidine or diethylamine in the presence of formalin in DMF (Scheme 1). We now report the synthesis of 6,8-diarylimino-7*H*-pyrano [3,2-*c*:5,6-*c′*]dicoumarins **3** and their conversion into the corresponding dicoumarins **4** which belong to the class of nonpeptidic HIV protease inhibitors.[10]

On heating dichromones **2** in $POCl_3$ at 60–80 °C for 5–6 h subsequent work-up produced diiminocoumarins **3** in moderate yields. The structure of the compounds was established on the basis of IR, $^1$H and $^{13}$C NMR and mass spectral analyses. Formation of **3** may be rationalised by considering the initial attack of the vinylogous amide moiety in **2** on $POCl_3$ to produce **5** which cyclises readily by the involvement of the second vinylogus amide group (Scheme 1).

In an attempt to convert the central pyran ring in **3** into a pyridine ring, compound **3a** was heated with urea in AcOH for 1 h. But surprisingly, compound **3a** only gave **2a**. The same reaction took place when **3** was heated with ammonium acetate




**Scheme 1**

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**Table 1** Chemoselective hydrolysis of **3** under different conditions

| Entry | $R^1$ | $R^2$ | Method | Product | Yield / % | M.p./ °C (lit. M.p./ °C) |
|---|---|---|---|---|---|---|
| 1 | H | Ph | A | **2b** | 80 | 300–302 (300–302) [9] |
| 2 | H | Ph | B | **4b** | 70 | 322–324 (321–323)[11] |
| 3 | H | Ar[a] | A | **2c** | 78 | 314–316 |
| 4 | H | Ar | B | **4b** | 72 | 322–324 |
| 5 | Me | Ph | A | **2a** | 77 | 268–270 (268–270) [9] |
| 6 | Me | Ph | B | **4a** | 66 | >325 |
| 7 | Me | Ar | A | **2d** | 77 | 304–306 (304–306) [9] |
| 8 | Me | Ar | B | **4a** | 70 | >325 |

[a]Ar = 4-$MeC_6H_4$.
Method A: AcOH, reflux, 30 min.
Method B: HCl/MeOH, reflux, 30 min.

in acetic acid or with thiourea in acetic acid. It appeared to be a case of acid-catalysed hydrolysis of the central pyran ring and AcOH was supposed to be responsible for this reversion. Indeed, compound **3** gave **2** in good yields when heated in glacial AcOH for only 0.5 h (Scheme 1, Method A) (Table 1, entries 1, 3, 5 and 7).

Regarding the synthesis of 7*H*-pyrano[3,2-*c*:5,6-*c*′] dicoumarins **4**, an earlier report revealed that dicoumarol cyclises to **4** on treatment with $(PhO)_2POCl$/pyridine or $KHSO_4$ or $P/I_2$.[11] Dicoumarols derived from 4-hydroxycoumarin and an aldehyde other than formaldehyde can be cyclised to **4** (having a substituent at its 7-position) by pyridine-acetic anhydride.[12] Diglucosides of dicoumarol also produce **4** and glucose when treated with $Ba(OCH_3)_2$ in methanol.[13] All these methods have shortcomings due to harsh reaction conditions, tedious work-up or poor yields. The synthesis of **3** gave us an impetus to check whether **4** can be obtained from **3** by chemoselective hydrolysis. In compound **3**, the arylimino functions and the ether linkage are susceptible towards hydrolysis. The ether function was found to hydrolyse selectively by heating in acetic acid (Table 1, entries 1, 3, 5 and 7). To hydrolyse the arylimino function, mineral acid was considered. Indeed, compound **4** was obtained in good yield by heating **3** in methanol in the presence of HCl (Scheme 1, Method B) (Table 1, entries 2, 4, 6 and 8).

In conclusion, we have achieved an easy route for the synthesis of 6,8-diarylimino-7*H*-pyrano[3,2-*c*:5,6-*c*′]dicoumarins **3** and their chemoselective hydrolysis to 3,3′-methylenedi (2-arylamino-4*H*-chromen-4-ones) **2** and 7*H*-pyrano[3,2-*c*:5,6-*c*′]dicoumarins **4**.

## Experimental

The recorded melting points are uncorrected. IR spectra were recorded in KBr on a Beckman IR 20A spectrophotometer. $^1H$ and $^{13}C$ NMR spectra were obtained on a Bruker spectrometer at 300 MHz and 75 MHz respectively. Mass spectra were recorded on a Qtof Micro YA 263 instrument and elemental analysis on a Perkin Elmer 240c elemental analyser. Light petroleum refers to the fraction with b.p. 60–80 °C. All chemicals used were of commercial grade and were used as such.

*Reaction of dichromone **2** with $POCl_3$; general procedure*
Dichromone **2** (1 mmol) was heated with $POCl_3$ (10 mL) in an oil bath at 60–80 °C for 5–6 h. The reaction mixture was cooled to room temperature and poured into crushed ice (100 g). The separated solid was filtered, washed with water, dried in air and crystallised from benzene-light petroleum (6:1) to afford **3**.

*2,12-Dimethyl-6,8-di(*N-*phenylimino)-7*H-*pyrano[3,2-*c*:5,6-*c*′] dicoumarin* (**3a**): Pale yellow crystalline solid (285 mg, 57%); m.p. 266–268 °C; IR: $\nu_{max}$ 3029, 1676, 1643, 1584 $cm^{-1}$; $^1H$ NMR: δ ($CDCl_3$) 2.39 (6 H, s, 2 × $CH_3$), 3.42 (2 H, s, $CH_2$), 6.91 (2 H, br. d, *J* = 7.2 Hz, ArH), 7.10–7.16 (2 H, m, ArH), 7.21–7.24 (4 H, m, ArH), 7.28–7.39 (6 H, m, ArH), 7.50 (2 H, br. s, 1-H + 13-H); $^{13}C$ NMR: δ 20.4, 21.0, 105.0, 114.5, 115.6, 121.3, 123.3, 123.6, 128.3, 128.5, 133.2, 146.5, 147.9, 148.6, 150.6; MS (Positive ion electrospray): *m/z* 497 $[M+H]^+$, 519 $[M+Na]^+$. Anal. Calcd for $C_{33}H_{24}N_2O_3$: C, 79.82; H, 4.87; N, 5.64. Found: C, 79.53; H, 4.79; N, 5.56%.

*6,8-Di(*N-*phenylimino)-7*H-*pyrano[3,2-*c*:5,6-*c*′]dicoumarin* (**3b**): Pale yellow crystalline solid (295 mg, 63%); m.p. > 320 °C; IR: $\nu_{max}$ 3010, 1680, 1650, 1560 $cm^{-1}$; $^1H$ NMR: δ ($CDCl_3$) 3.62 (2 H, s, $CH_2$), 7.10–7.15 (4 H, m, ArH), 7.19–7.29 (6 H, m, ArH), 7.31–7.47 (6 H, m, ArH), 7.87 (2 H, br. d, *J* = 7.8 Hz, 1-H + 13-H); MS (Positive ion electrospray): *m/z* 469 $[M+H]^+$, 491 $[M+Na]^+$. Anal. Calcd for $C_{31}H_{20}N_2O_3$: C, 79.47; H, 4.30; N, 5.98. Found: C, 79.33; H, 4.22; N, 5.90%.

*6,8-Di[*N-*(4-methylphenyl)imino]-7*H-*pyrano[3,2-*c*:5,6-*c*′]dicoumarin* (**3c**): Pale yellow fine crystalline solid (225 mg, 45%); m.p. 252–254 °C; IR: $\nu_{max}$ 3014, 1672, 1640, 1570 $cm^{-1}$; $^1H$ NMR: δ ($CDCl_3$) 2.37 (6 H, s, 2 × $CH_3$), 3.57 (2 H, s, $CH_2$), 7.12 (2 H, br. d, *J* = 8.1 Hz, 4-H + 10-H), 7.13–7.19 (6 H, m, ArH), 7.23–7.28 (4 H, m, ArH), 7.39–7.44 (2 H, m, 3-H + 11-H), 7.82 (2 H, br. d, *J* = 7.5 Hz, 1-H + 13-H); $^{13}C$ NMR: 20.4, 21.0, 105.1, 114.8, 115.9, 121.4, 123.2, 123.5, 129.2, 130.9, 133.2, 143.5, 147.7, 148.2, 152.4. Anal. Calcd for $C_{33}H_{24}N_2O_3$: C, 79.82; H, 4.87; N, 5.64. Found: C, 79.69; H, 4.80; N, 5.50%.

*2,12-Dimethyl-6,8-di[*N-*(4-methylphenyl)imino]-7*H-*pyrano[3,2-*c*:5,6-*c*′]dicoumarin* (**3d**): Yellow fine crystalline solid (245 mg, 47%); m.p. 280–282 °C; IR: $\nu_{max}$ 3000, 1680, 1640, 1590 $cm^{-1}$; $^1H$ NMR: δ ($CDCl_3$) 2.36 (6 H, s, 2 × $CH_3$), 2.46 (6 H, s, 2 × $CH_3$), 3.55 (2 H, s, $CH_2$), 7.01 (2 H, d, *J* = 8.4 Hz, 4-H + 10-H), 7.16–7.19 (8 H, m, ArH), 7.21 (2 H, br. d, *J* = 8.4 Hz, 3-H + 11-H), 7.59 (2 H, br. s, 1-H + 13-H). Anal. Calcd for $C_{35}H_{28}N_2O_3$: C, 80.13; H, 5.38; N, 5.34. Found: C, 79.95; H, 5.28; N, 5.26%.

*Synthesis of 7*H-*pyrano[3,2-c:5,6-c′]dicoumarins* **4** *by hydrolysis of* **3**
Four drops of conc. HCl were added to a methanolic suspension (25 mL) of **3** (1 mmol), at room temperature whereupon an orange-yellow coloured, clear solution was formed. The resultant solution was heated under reflux for 0.5 h; a white solid separated. The product was filtered whilst hot, washed with methanol and crystallised from benzene-light petroleum (2:1) to afford **4** in good yield. Compounds **3a** and **3d** produced the same compound, **4a** in 66 and 70% yields, respectively; similarly compounds **3b** and **3c** produced **4b** in 70 and 72% yields, respectively.

*2,12-Dimethyl-7*H-*pyrano[3,2-*c*:5,6-*c*′]dicoumarin* (**4a**): White crystalline solid (250 mg, 72%); m.p. > 325 °C; $\nu_{max}$ 2987, 2910, 1725, 1630, 1590 $cm^{-1}$; $^1H$ NMR: δ ($CDCl_3$) 2.55 (6 H, s, 2 × $CH_3$), 3.57 (2 H, s, $CH_2$), 7.31 (2 H, d, *J* = 7.8 Hz, 4-H + 10-H), 7.44 (2 H, br. d, *J* = 7.8 Hz, 3-H + 11-H), 7.73 (2 H, br. s, 1-H + 13-H); MS (Positive ion electrospray): *m/z* 347 $[M+H]^+$, 369 $[M+Na]^+$. Anal. Calcd for $C_{21}H_{14}O_5$: C, 72.83; H, 4.07. Found: C, 72.66; H, 3.98%.

*7*H-*Pyrano[3,2-c:5,6-c′]dicoumarin* (**4b**): White crystalline solid (250 mg, 78%); m.p 322–324 °C (lit[11] m.p. 321–323 °C); $\nu_{max}$ 3060, 2924, 1724, 1619, 1586 $cm^{-1}$; $^1H$ NMR: δ ($CDCl_3$) 3.61 (2 H, s, $CH_2$), 7.38–7.48 (4 H, m, ArH), 7.61–7.69 (2 H, m, 3-H + 11-H), 7.99 (2 H, dd, *J* = 7.8, 1.5 Hz, 1-H + 13-H); $^{13}C$ NMR: 18.5, 102.1, 113.3, 117.2, 122.1, 124.6, 132.7, 152.5, 154.2, 179.6. Anal. Calcd for $C_{19}H_{10}O_5$: C, 71.70; H, 3.17. Found: C, 71.58; H, 3.25%.

*Hydrolysis of **3** to produce **2***
Compound **3** (1 mmol) was heated in glacial acetic acid (15 mL) for 0.5 h under reflux. On cooling, the reaction mixture afforded a white solid. The precipitated solid was filtered off, washed with methanol, dried in air and crystallised from benzene-petroleum ether (10:1) to afford **2a–d**, which were found to be identical in all respects with the corresponding compounds **2** from which compound **3** was obtained by treatment with $POCl_3$.

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