One-pot three component reaction for the synthesis of chromone-linked naphthopyrans

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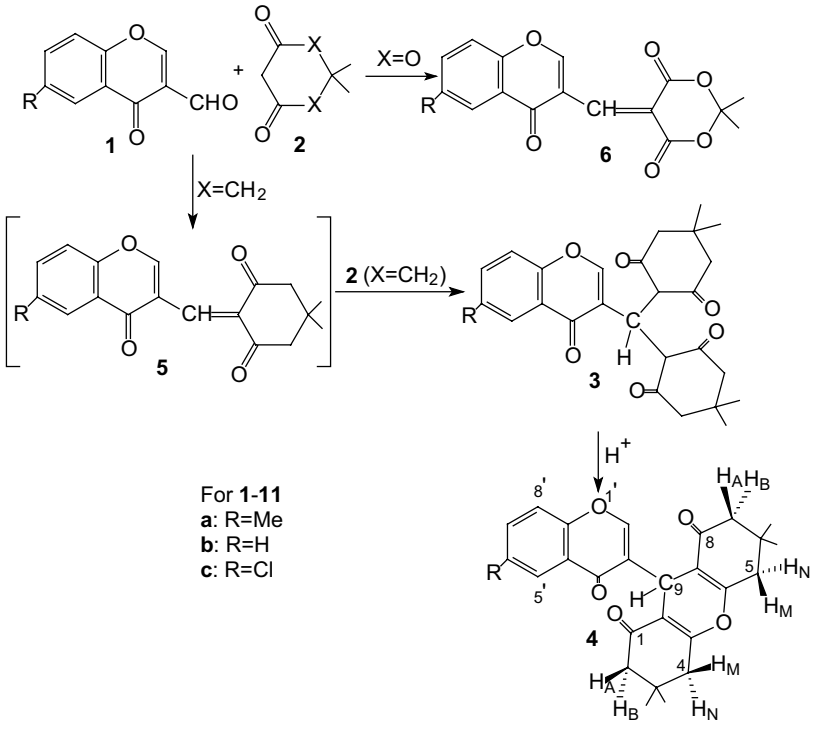
Heating an equimolar mixture of 6-substituted chromone-3-carbaldehydes, β-naphthol and dimedone in AcOH produces 3,3-dimethyl-11-(4-oxo-4*H*-1-benzopyran-3-yl)-1,2,3,4-tetrahydronaphtho[2,1-*b*]-1-benzopyran-11*H*-1-ones, whereas under similar condition use of Meldrum's acid in place of dimedone gave 1-benzopyrano[2,3-*b*]naphtho[1,2-*e*]pyran-7a*H*, 13*H*-13-ones and 3,4-dihydro-4-(4-oxo-4*H*-1-benzopyran-3-yl)naphtho[2,1-*b*]pyran-2*H*-2-ones.

Keywords: chromone-3-carbaldehyde, multicomponent reaction, dimedone, Meldrum's acid, 1-benzopyran

Multicomponent reactions (MCR) are a powerful tool for the synthesis of various heterocycles.[1-3] Dimedone and Meldrum's acid have shown their wide application in organic synthesis. Dimedone exists in chair conformation and is significantly enolised in solution, whereas Meldrum's acid does not undergo enolisation in solution or in the solid state to a significant extent and exists preferentially in a boat conformation. The C–H acidity of Meldrum's acid is very high compared to dimedone.[4-6] Despite such basic differences, both these compounds react as active methylene component in MCR. Dimedone reacts with aldehydes in the presence of $CH_2(CN)_2$,[7-12] $PhNHCH_2COPh$,[13] β-naphthol,[14] 2-amino-4-phenylpyrrole,[15] to afford various heterocycles. Meldrum's acid similarly reacts with aldehydes in the presence of phloroglucinol to produce dihydrocoumarin.[16] Although the condensate of an aldehyde and Meldrum's acid can react with phenol in the presence of $Yb(OTf)_3$ to produce 3,4-dihydrocoumarin,[17] a similar condensate of an aldehyde and dimedone could not be isolated.

The chromone moiety is an important component of a number of pharamaceuticals.[18] 3-Formylchromone **1** is not only a very useful compound in synthesis due to the presence of three electrophilic centres, but also exhibits cytotoxicity against cancer cells.[19] The reaction of **1** with dimedone or Meldrum's acid have been studied. It was reported that dimedone **2** (X = CH_2) reacted with **1** to produce **3**,[20] which undergoes acid catalysed cyclisation to **4**.[21] In no case could the Knoevenagel condensate **5** be isolated, whereas **1** reacted with Meldrum's acid **2** (X = O) to produce the condensate **6**[22-24] (Scheme 1). Compound **3** is expected to form by a Michael-addition of dimedone on condensate **5**, so it may be possible to trap the condensate **5** by employing a suitable nucleophile in the reaction medium. To the best of our knowledge, the only report[25] of this type appeared in the literature is the reaction of **1** with dimedone in the presence of ethyl acetoacetate and NH_4OAc to produce ethyl 4-(4-oxo-4*H*-1-benzopyran-3-yl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-3-quinolinecarboxylate. Our objective was to study the mode of reactions of dimedone and Meldrum's acid with **1** in the presence of phenolic compounds.

Heating an equimolar mixture of **1**, **2** (X = CH_2) and β-naphthol in acetic acid at 60–80 °C for 8 h produced **7** in moderate yield. The structure of the compound was established on the basis of IR, ^1H NMR and mass spectral analysis.



Scheme 1

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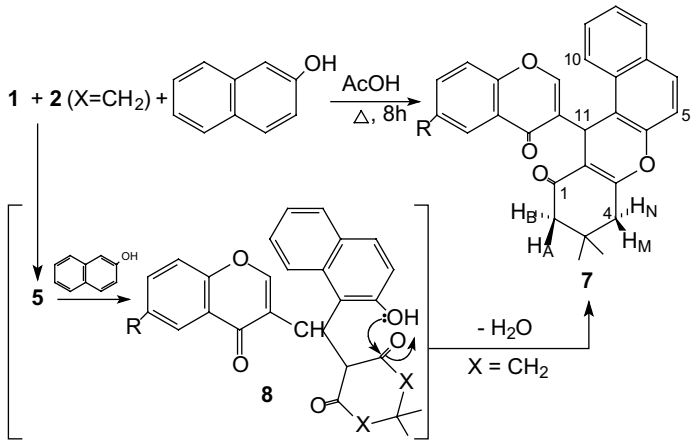


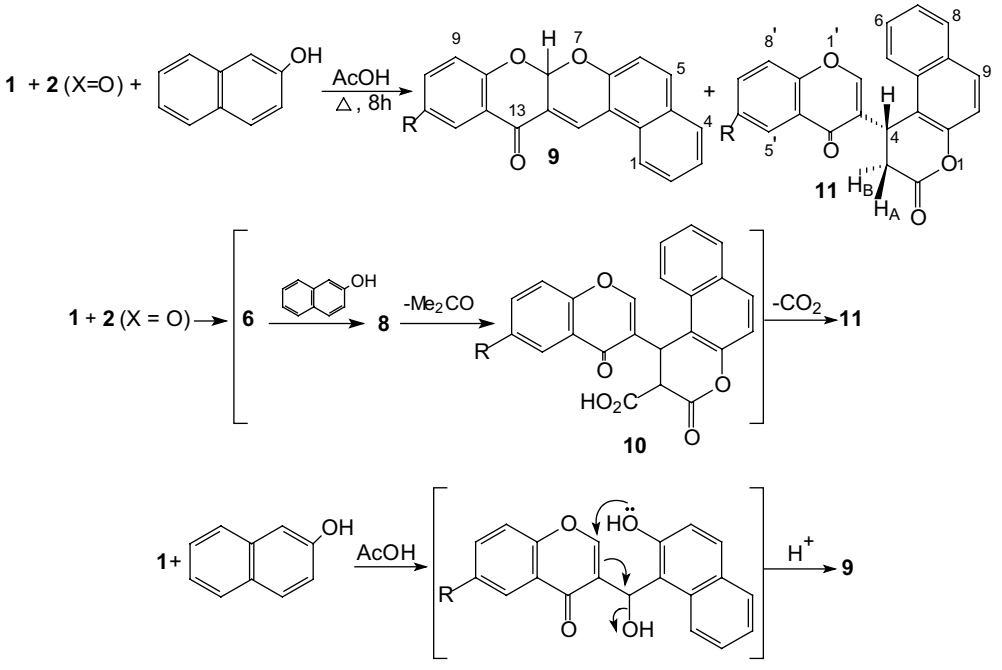
Scheme 2

The formation of **7** may be explained *via* the formation of condensate **5**, which is intercepted by β-naphthol to form **8** (X = CH_2). Subsequent cyclisation of **8** (X = CH_2) followed by dehydration leads to the formation of **7** (Scheme 2). To check the formation of **5**, a mixture of **1** and **2** (X =CH_2) in 1 : 1 molar proportion was heated for 7 h in ethanol in the presence of catalytic amount of pyridine. After usual work up, the product isolated was found to be **4**.[21] Compound **4** was also obtained when the same reaction was carried out in acetic acid alone instead of ethanol in the presence of pyridine.

The above reaction was repeated using *p*-cresol instead of β-naphthol, but *p*-cresol failed to trap the condensate **5**. On heating **1**, **2** (X = CH_2) and *p*-cresol in equimolar amounts in acetic acid, compound **4** was the only isolated product (20%). The use of acetylacetone in place of *p*-cresol also yielded compound **4** as the only isolated pure product but in a very poor yield (5%).

In view of the higher nucleophilicity of β-naphthol in trapping the condensate **5**, an equimolar mixture of **1**, **2** (X = O) and β-naphthol was heated in acetic acid at 60–80 °C for 8 h. The reaction mixture produced a yellow compound **9** and a white compound **11**. Structures of compounds **9** and **11** were established on the basis of IR, ^{1}H NMR and mass spectral analysis. The formation of **11** may be rationalised as follows: condensate **6**, obtained from **1** and **2** (X = O), reacted with β-naphthol to form **8** (X = O). Cyclisation of **8** (X = O) with the expulsion of acetone molecule produced **10**, which on subsequent decarboxylation produced **11** (Scheme 3).

The structure of **9** indicates the direct interaction between **1** and β-naphthol. For verification, an equimolar mixture of **1** and β-naphthol was heated at 60–80 °C in acetic acid, and, indeed, compound **9** was obtained in moderate yields. It is to be mentioned here that the reaction of **1** and β-naphthol in 1:2 molar ratio in acetic acid in the presence of trace amount of HCl produced a bridge compound.[26,27] The formation of **9** from the reaction mixture of **1**, **2** (X = O) and β-naphthol led us to repeat the reaction of **1**, **2** (X =CH_2) and β-naphthol. After isolation of compound **7**, the filtrate showed the presence of **9** (by TLC). On chromatographic separation, the filtrate afforded **9** in only 2% yield when eluted with 25% benzene in light-petroleum, whereas 15–20% of **9** was isolated from the reaction mixture involving Meldrum's acid. The difference in the yield of **9** in these two reactions may be due to higher reactivity of dimedone over Meldrum's acid



Scheme 3

towards **1**. Higher enol-content of dimedone over Meldrum's acid is responsible for the difference in reactivity towards **1** in acid medium.

In conclusion, we have synthesised some hitherto unreported chromone-linked and chromone-fused naphthopyrans involving dimedone and Meldrum's acid as active methylene component. Differences in the yield of chromone-fused naphthopyran ring **9** in the reaction of **1**, **2** (X = CH_2, O) and β–naphthol has been rationalised in the light of the higher enol-content of dimedone over Meldrum's acid.

Experimental

IR spectra were recorded in KBr on a Beckman IR 20A instrument, ^{1}H NMR spectra in $CDCl_3$ on a Bruker 300 MHz spectrometer, mass spectra on a Qtof Micro YA 263 instrument and elemental analysis on a Perkin Elmer 240C elemental analyser. Light petroleum refers to the fraction with distillation range 60–80 °C.

Reaction of chromone-3-carbaldehyde (**1**) *with dimedone in presence of* β*-naphthol; general procedure*

A mixture of **1** (1 mmol), **2** (X = CH_2) (140 mg, 1 mmol) and β-naphthol (144 mg, 1 mmol) was heated in acetic acid (10 mL) at 60–80 °C for 8 h. On cooling, the reaction mixture afforded a solid, which was filtered, washed with water, dried in air and recrystallised from chloroform-light petroleum (40–60 °C) to afford **7**.

3,3-Dimethyl-11-(6-methyl-4-oxo-4H-1-benzopyran-3-yl)-1,2,3,4-tetrahydronaphtho[2,1-b]-1-benzopyran-11H-1-one (**7a**): White crystalline solid (260 mg, 60%), m.p. 258 °C, IR: ν_{max} 2955, 1650, 1620, 1484 cm^{-1}; ^{1}H NMR: δ 1.02 (3 H, s, 3-CH_3), 1.12 (3 H, s, 3-CH_3), 2.24 (1 H, d, *J* = 16.8 Hz, H_N), 2.30 (3 H, s, 6'-CH_3), 2.33 (1 H, d, *J* = 16.8 Hz, H_M), 2.56 (1 H, d, *J* = 17.4 Hz, H_B), 2.66 (1 H, d, *J* = 17.4 Hz, H_A), 5.60 (1 H, s, 11-H), 7.21 (1 H, d, *J* = 7.8 Hz, 8'-H), 7.25–7.33 (3 H, m, ArH), 7.43–7.46 (1 H, m, ArH), 7.71–7.76 (2 H, m, ArH), 7.83 (1 H, brs, 5'-H), 8.08 (1 H, d, *J* = 7.8 Hz, 7-H), 8.27 (1 H, s, 2'-H). MS (positive ion electrospray): *m/z* 437 (M + H$^+$), 459 (M + Na$^+$). Anal. Calcd for $C_{29}H_{24}O_4$: C, 79.80; H, 5.54. Found: C, 79.65; H, 5.45%.

3,3-Dimethyl-11-(4-oxo-4H-1-benzopyran-3-yl)-1,2,3,4-tetrahydronaphtho[2,1-b]-1-benzopyran-11H-1-one (**7b**): White crystalline solid (260 mg, 62%), m.p. 282–284 °C, IR: ν_{max} 2970, 1640, 1630, 1596 cm^{-1}; ^{1}H NMR: δ 1.03 (3 H, s, 3-CH_3), 1.13 (3 H, s, 3-CH_3), 2.25 (1 H, d, *J* = 16.5 Hz, H_N), 2.34 (1 H, d, *J* = 16.5 Hz, H_M), 2.58 (1 H, d, *J* = 17.4 Hz, H_B), 2.69 (1 H, d, *J* = 17.4 Hz, H_A), 5.60 (1 H, s, 11-H), 7.23–7.39 (4 H, m, ArH), 7.45–7.56 (2 H, m, ArH), 7.73–7.79 (2 H, m, ArH), 8.05–8.10 (2 H, m, ArH), 8.31 (1 H, s, 2'-H). MS (positive ion electrospray): *m/z* 423 (M + H$^+$), 445 (M + Na$^+$). Anal. Calcd for $C_{28}H_{22}O_4$: C, 79.60; H, 5.25. Found: C, 79.44; H, 5.09%.

3,3-Dimethyl-11-(6-chloro-4-oxo-4H-1-benzopyran-3-yl)-1,2,3,4-tetrahydronaphtho[2,1-b]-1-benzopyran-11H-1-one (**7c**): White crystalline solid (300 mg, 66%), m.p. 286–288 °C, IR: ν_{max} 3010, 1645, 1620, 1500 cm^{-1}; ^{1}H NMR: δ 1.03 (3 H, s, 3-CH_3), 1.14 (3 H, s, 3-CH_3), 2.25 (1 H, d, *J* = 16.5 Hz, H_N), 2.34 (1 H, d, *J* = 16.5 Hz, H_M), 2.58 (1 H, d, *J* = 17.4 Hz, H_B), 2.68 (1 H, d, *J* = 17.4 Hz, H_A), 5.60 (1 H, s, 11-H), 7.28–7.39 (3 H, m, ArH), 7.45–7.48 (2 H, m, ArH), 7.73–7.79 (2 H, m, ArH), 8.02 (1 H, brs, 5'-H), 8.06 (1 H, d, *J* = 8.0 Hz, 7-H), 8.31 (1 H, s, 2'-H). Anal. Calcd for $C_{28}H_{21}ClO_4$: C, 73.60; H, 4.63. Found: C, 73.69; H, 4.74%.

Treatment of chromone-3-carbaldehyde ***1*** *with dimedone* ***2*** *(X = CH_2)*: An ethanolic solution (25 mL) of a mixture of **1** (1 mmol) and **2** (X = CH_2) (140 mg, 1 mmol) was heated under reflux for 7 h in the presence of pyridine (2 drops). The resultant red solution was concentrated under reduced pressure. Ice-water (10 g) was added to the concentrate when an oily substance appeared. It was extracted with chloroform (2 × 10 mL), washed with water, dried over Na_2SO_4. On concentration, the $CHCl_3$ solution afforded a white crystalline solid **4**.

1,2,3,4,5,6,7,8-Octahydro-3,3,6,6-tetramethyl-9-(6-methyl-4-oxo-4H-1-benzopyran-3-yl)-9H-xanthene-1,8-dione (**4a**): White crystalline solid, (100 mg, 46%), m.p. 298–300 °C. IR: ν_{max} 2957, 1680, 1654, 1483 cm^{-1}; ^{1}H NMR: δ 0.98 (6 H, s, 2 × CH_3), 1.09 (6 H, s, 2 × CH_3), 2.17 (2 H, d, *J* = 16.4 Hz, 2 × H_N), 2.24 (2 H, d, *J* = 16.4 Hz, 2 × H_M), 2.39 (3 H, s, ArCH_3), 2.42 (2 H, d, *J* = 17.4 Hz, 2 × H_B), 2.55 (2 H, d, *J* = 17.4 Hz, 2 × H_A), 4.50 (1 H, s, 9-H), 7.28 (1 H, d, *J* = 7.8 Hz, 8'-H), 7.39 (1 H, brd, *J* = 7.8 Hz, 7'-H), 7.86 (1 H, brs, 5'-H), 8.22 (1 H, s, 2'-H). Anal. Calcd for $C_{27}H_{28}ClO_5$: C, 74.98; H, 6.53. Found: C, 75.10; H, 6.61%.

1,2,3,4,5,6,7,8-Octahydro-3,3,6,6-tetramethyl-9-(4-oxo-4H-1-benzopyran-3-yl)-9H-xanthene-1,8-dione (**4b**): White crystalline solid, (110 mg, 52%), m.p. 285–287 °C (lit.[21] m.p. 287–288 °C). IR: ν_{max} 2950, 1670, 1653, 1484 cm^{-1}; ^{1}H NMR: δ 0.97 (6 H, s, 2 × CH_3), 1.09 (6 H, s, 2 × CH_3), 2.17 (2 H, d, *J* = 16.5 Hz, 2 × H_N), 2.24 (2 H, d, *J* = 16.5 Hz, 2 × H_M), 2.43 (2 H, d, *J* = 17.7 Hz, 2 × H_B), 2.55 (2 H, d, *J* = 17.7 Hz, 2 × H_A), 4.50 (1 H, s, 9-H), 7.30–7.38 (2 H, m, 6'-H and 8'-H), 7.56–7.61 (1 H, m, 7'-H), 8.08 (1 H, brd, *J* = 7.8 Hz, 5'-H), 8.25 (1 H, s, 2'-H).

The same reaction was also carried out in acetic acid. A mixture of **1a** (188 mg, 1 mmol) and **2** (X = CH_2) (140 mg, 1 mmol) in acetic acid (10 mL) was heated at 60–80 °C for 8 h. On cooling, the reaction mixture afforded a solid, which on crystallisation produced **4a** (110 mg, 51%).

Reaction of chromone-3-carbaldehyde (**1**) *with Meldrum's acid in presence of* β*-naphthol; general procedure*

A mixture of **1** (1 mmol), **2** (X = O)(144 mg, 1 mmol) and β-naphthol (144 mg, 1 mmol) was heated at 60–80 °C in acetic acid (10 mL) for 8 h. Solvent was removed under reduced pressure. Ice-water (10 g) was added to the residue, a semisolid mass appeared, which was extracted with chloroform (2 × 10 mL), washed with water (2 × 15 mL) and dried over Na_2SO_4. The resultant chloroform solution was chromatographed over silica gel (100–200) using benzene containing varying amounts of light petroleum as eluent. Compound **9** was isolated using 25% benzene in light petroleum and 50% benzene in light petroleum afforded **11**.

11-Methyl-1-benzopyrano[2,3-b]naphtho[1,2-e]pyran-7aH, 13H-13-one (**9a**): Yellow solid (60 mg, 19%); m.p. 172–174 °C. IR: ν_{max} 2930, 1680, 1635, 1573, 1488 cm^{-1}; ^{1}H NMR: δ 2.36 (3 H, s, ArCH_3), 6.93 (1 H, s, 7a-H), 7.05 (1 H, d, *J* = 8.0 Hz, 9-H), 7.25 (1 H, d, *J* = 8.1 Hz, 6-H), 7.38–7.47 (2 H, m, ArH), 7.57–7.62 (1 H, m, ArH), 7.80 (1 H, brd, *J* = 8.1 Hz, 5-H), 7.82 (1 H, brs, 12-H), 7.87 (1 H, brd, *J* = 9.0 Hz, 1-H), 8.14 (1 H, brd, *J* = 8.4 Hz, 4-H), 8.34 (1 H, s, 14-H). MS (positive ion electrospray): *m/z* 315 (M + H$^+$), 337(M + Na$^+$). Anal. Calcd for $C_{21}H_{14}O_3$: C, 80.24; H, 4.49. Found: C, 79.95; H, 4.60%.

1-Benzopyrano[2,3-b]naphtho[1,2-e]pyran-7aH, 13H-13-one (**9b**): Yellow solid (50 mg, 17%); m.p. 194–196 °C, IR: ν_{max} 3000, 1670, 1640, 1550, 1500 cm^{-1}; ^{1}H NMR: δ 6.98 (1 H, s, 7a-H), 7.14–7.19 (2 H, m, ArH), 7.24–7.27 (1 H, m, ArH), 7.43–7.48 (1 H, m, ArH), 7.57–7.64 (2 H, m, ArH), 7.80 (1 H, brd, *J* = 8.1 Hz, 5-H), 7.88 (1 H, brd, *J* = 9.0 Hz, 1-H), 8.04 (1 H, brd, *J* = 7.8 Hz, 12-H), 8.15 (1 H, brd, *J* = 8.4 Hz, 4-H), 8.35 (1 H, s, 14-H). MS (positive ion electrospray): *m/z* 301 (M + H$^+$), 323 (M + Na$^+$). Anal. Calcd for $C_{20}H_{12}O_3$: C, 79.99; H, 4.03. Found: C, 80.12; H, 3.95%.

11-Chloro-1-benzopyrano[2,3-b]naphtho[1,2-e]pyran-7aH, 13H-13-one (**9c**): Yellow solid (65 mg, 19%); m.p. 224–226 °C, IR: ν_{max} 2950, 1660, 1640, 1560, 1480 cm^{-1}; ^{1}H NMR: δ 6.96 (1 H, s, 7a-H), 7.10 (1H, d, *J* = 8.4 Hz, 9-H), 7.24 (1 H, d, *J* = 7.8 Hz, 6-H), 7.44–7.53 (2 H, m, ArH), 7.60–7.64 (1 H, m, ArH), 7.81 (1 H, d, *J* = 7.8 Hz, 5-H), 7.90 (1 H, brd, *J* = 8.7 Hz, 1-H), 7.98 (1 H, brs, 12-H), 8.14 (1 H, d, *J* = 8.4 Hz, 4-H), 8.36 (1 H, s, 14-H). Anal. Calcd for $C_{20}H_{11}ClO_3$: C, 71.76; H, 4.03. Found: C, 71.55; H, 4.14%.

3,4-Dihydro-4-(6-methyl-4-oxo-4H-1-benzopyran-3-yl) naphtho[2,1-b]pyran-2H-2-one (**11a**): White crystalline solid (100 mg, 28%), m.p. 184–186 °C. IR: ν_{max} 3068, 1777, 1636, 1621, 1485 cm^{-1}; ^{1}H NMR: δ 2.48 (3 H, s, ArCH_3), 3.13 (1 H, dd, *J* = 16.2, 6.9 Hz, H_B), 3.37 (1 H, d, *J* = 16.2 Hz, H_A), 5.31 (1 H, d, *J* = 6.9 Hz, 4-H), 7.14 (1 H, s, 2'-H), 7.25 (1 H, brd, *J* = 8.1 Hz, 8-H), 7.34 (1 H, brd, *J* = 8.7 Hz, 5-H), 7.46–7.52 (3 H, m, ArH), 7.74 (1 H, brd, *J* = 8.1 Hz, 7'-H), 7.88–7.91 (2 H, m, ArH), 8.08 (1 H, brs, 5'-H). MS (positive ion electrospray): *m/z* 357 (M + H$^+$), 379 (M + Na$^+$). Anal. Calcd for $C_{23}H_{16}O_4$: C, 77.52; H, 4.53. Found: C, 77.38; H, 4.44%.

3,4-Dihydro-4-(4-oxo-4H-1-benzopyran-3-yl)naphtho[2,1-b] pyran-2H-2-one (**11b**): White crystalline solid (110 mg, 32%), m.p. 194–196° C. IR: ν_{max} 3050, 1770, 1640, 1615, 1470 cm^{-1}; ^{1}H NMR: δ 3.13 (1H, dd, *J* = 16.2, 7.2 Hz, H_B), 3.38 (1 H, d, *J* = 16.2 Hz, H_A), 5.32 (1 H, d, *J* = 7.2 Hz, 4-H), 7.16 (1 H, s, 2'-H), 7.34–7.37 (2 H, m, ArH), 7.43–7.51 (3 H, m, ArH), 7.64–7.69 (1 H, m, ArH), 7.75 (1 H, d, *J* = 7.5 Hz, 9-H), 7.89–7.92 (2 H, m, ArH), 8.31 (1 H, brd, *J* = 7.8 Hz, 5'-H). MS (positive ion electrospray): *m/z* 343 (M + H$^+$), 365 (M + Na$^+$). Anal. Calcd for $C_{22}H_{14}O_4$: C, 77.18; H, 4.12. Found: C, 77.08; H, 3.99%.

3,4-Dihydro-4-(6-chloro-4-oxo-4H-1-benzopyran-3-yl)naphtho-[2,1-b]pyran-2H-2-one (**11c**): White crystalline solid, (110 mg, 29%), m.p. 214–216 °C. IR: ν_{max} 3020, 1760, 1635, 1620, 1480 cm^{-1}; ^{1}H NMR: δ 3.13 (1 H, dd, *J* = 16.2, 6.9 Hz, H_B), 3.37 (1 H, d, *J* = 16.2 Hz, H_A), 5.29 (1 H, d, *J* = 6.9 Hz, 4-H), 7.15 (1 H, s, 2'-H), 7.26–7.36 (2 H, m, ArH), 7.48–7.54 (2 H, m, ArH), 7.60 (1 H, brd, *J* = 8.7 Hz, 5-H), 7.73 (1 H, d, *J* = 7.5 Hz, 9-H), 7.89–7.92 (2 H, m, ArH), 8.26 (1 H, brs, 5'-H). Anal. Calcd for $C_{22}H_{13}ClO_4$: C, 70.13; H, 3.48. Found: C, 69.97; H, 3.35%.

Synthesis of **9** *from* **1**: An equimolar mixture of **1** (1 mmol) and β–naphthol (144 mg, 1 mmol) in AcOH (5 mL) was heated at 60–80 °C for 8 h. The resultant mixture was poured into crushed ice (20 g). The yellow solid which separated was filtered off, washed with water, dried in air and recrystallised from chloroform-light petroleum (40–60 °C) to afford a yellow solid **9**. Compound **9a** (200 mg, 67%), **9b** (180 mg, 60%) and **9c** (210 mg, 63%) are identical in all respects to those produced from the reaction mixture of **1**, **2** (X = O) and β–naphthol.

We gratefully acknowledge CSIR, New Delhi [Project no. 01(2206)/07/EMR-II] for financial assistance; IICB, Jadavpur University, Jadavpur for spectral analysis and finally the college authority for providing research facilities.

Received 21 July 2009; accepted 19 October 2009
Paper 09/0693 doi: 10.3184/030823409X12561496499339
Published online: 17 November 2009

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