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# Reaction of sarcosine with chromone-3-carbaldehyde and 6,6'-(polymethylenedioxy)di(chromone-3-carbaldehyde)

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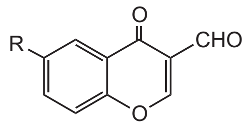
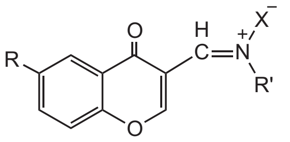
On treatment with *N*-methylglycine in DMF, the chromone-3-carbaldehydes **1a–c** produce 3-[3-(2-hydroxybenzoyl)-1-methyl-2,5-dihydropyrrol-2-yl]-4*H*-chromen-4-ones **10a–c** and the deformylated products **9a–c**, whereas the bis-chromone derivatives **12a–c** give the bis[3-(2-hydroxybenzoyl)-1-methylpyrrole] structures **13a–c**.

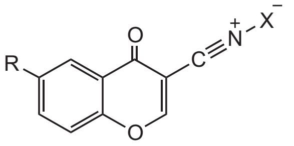
**Keywords:** chromone-3-carbaldehyde, pyrroles, sarcosine, bischromones, azomethine ylids



**1**



**2**, X = O
**4**, X = CH$_2$



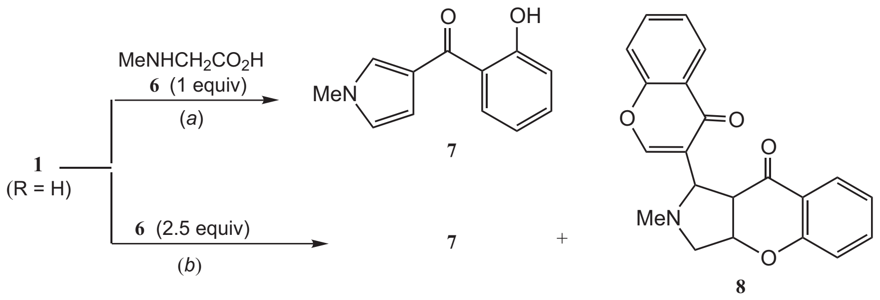
**3**, X = O
**5**, X = NR'

Reactions of 1,3-dipolar reagents **2**–**5** derived from chromone-3-carbaldehyde (**1**) have excited much attention because they open up a general avenue to the synthesis of many heterocycles linked to and fused with the pharmaceutically active chromone moiety. The nitrones **2** (R' = aryl),[1] nitrile imine **3**,[2] nitrile oxide **4**[3] have been prepared from **1**. Of these 1,3-dipolar reagents, the nitrones **2** (R' = aryl) have been studied in detail. The studied reactions include [3 + 2] cycloaddition reactions,[1,4] AlI$_3$-induced rearrangements[5] and thermal rearrangements.[6] A one-pot synthesis of nitrones **2** (R' = alkyl and aryl) from **1** and suitable nitroalkanes or nitroarenes,[7a] hydrolysis of **2**[7b] and their solvent dependent rearrangement [7c] have been reported from our laboratory.

With the idea of studying the rearrangement of azomethine ylides **5** derived from **1**, we decided to perform the reaction of *N*-methylglycine (sarcosine) (**6**) with **1**. Previous reports on this reaction include the use of equimolar amounts of **1** and **6** in toluene in the presence of catalytic amount of *p*-toluenesulfonic acid to produce **7** (Scheme 1).[8] The same reaction using 2.5 moles of **6** per mole of **1** in toluene without any catalyst has recently been reported to form **7** as major product along with a small amount of **8**.[9] However, the yield of **8** was improved by using a large excess of **1** over **6** (10:1). The trapping of the azomethine ylide **5** by C$_{60}$[10] and *N*-phenylmaleimide[9] are also reported. In the first report[8] on this reaction, the formation of azomethine ylide **5** was not considered. We have carried out the reaction in polar solvents. The results of the reaction of **6** with **1** and the corresponding di(chromone-3-carbaldehyde) **12** in polar solvents are reported herein.

A mixture of **1** (1 mmol) and **6** (3 mmol) in methanol was heated under reflux for 17 h, when the absence of starting material **1** was observed by TLC. Use of an equimolar mixture of **1** and **6** shows a little progress of the reaction even after heating for 10 h in methanol. Addition of **6** (2 mmol) more in this condition and heating for another 12 h completed the reaction. After usual work up and chromatographic separation, compound **9** (50%) and **10** (10%) were isolated. The major product **9** arises by base-catalysed deformylation of 1.[11] Formation of compound **10** may be rationalised by considering the initial formation of azomethine ylide intermediate **5**, which then undergoes [3 + 2] cycloaddition with another molecule of **1** to form **11**. This on deformylation followed by pyran ring opening produces **10**. To the best of our knowledge, this is the first example of the formation of a dihydropyrrole in these reactions.

To reduce the reaction time and to avoid deformylation, MeOH, which is low boiling, polar and protic, was replaced by the polar, aprotic and high boiling solvent DMF. The reaction was found to be complete in 7 h even after using equimolar amounts of **1** and **6**. However, after usual work-up and chromatographic separation, both the compounds **9** and **10** were obtained. Yield of **10** was found to increase considerably (from 10% to 35%) in changing the solvent from



*Conditions*: *a*, toluene, TsOH, 6h, Dean-Stark trap (ref. 8)
*b*, toluene, N$_2$ atm., 7.5 h (ref. 9)

**Scheme 1**

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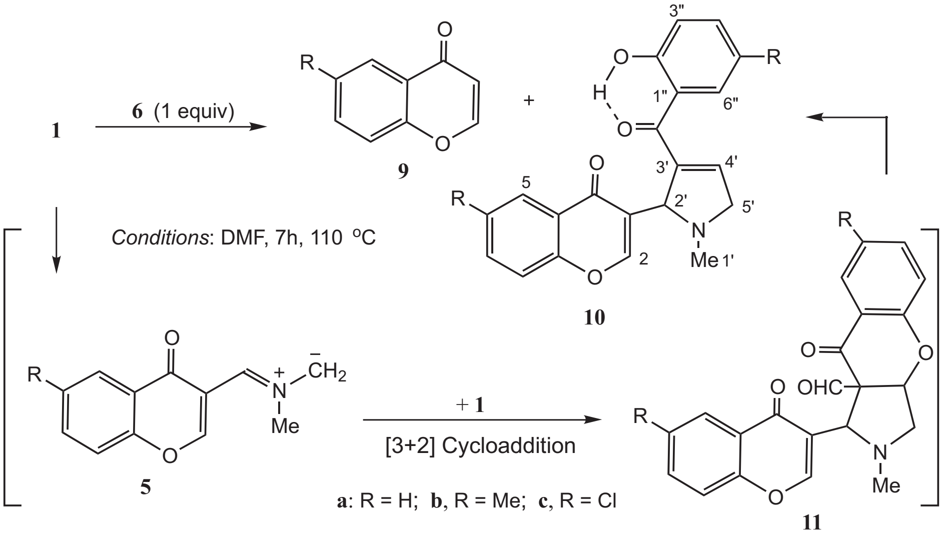


**Scheme 2**

MeOH to DMF. Using 2:1 molar ratio of **1** and **6**, completion of the reaction was not observed by TLC even after heating for 10 h at 110°C and after work-up, a trace amount of aldehyde **1** was isolated; no improvement in the isolated yield of **10** was observed. The proton from N-methylglycine **6** assists the formation of **9** by proto-deformylation in aprotic solvent. It should be mentioned here that compound **8**[9] (Scheme 1) was obtained following the same route as for the formation of **10** (Scheme 2), but without the opening of the pyran ring. Polar solvent facilitates the opening of the pyran ring.[7c]

Due to the poor solubility of **12** in toluene or methanol, the reaction of **12** with **6** was carried out in DMF. Moreover, on prolonged heating in MeOH, compound **12** was reported to form the corresponding acetal.[12] When a mixture of di(chromone-3-carbaldehyde) **12**[12] (1 mmol) and **6** (2 mmol) was heated in dry DMF for 7 h at 110°C (bath temperature), after usual work-up and chromatographic separation, the only isolated product was **13**, which is similar to the product **7** (Scheme 1),[8,9] obtained by heating a mixture of **1** and **6** in toluene. The reaction can be rationalised as follows: reaction of **12** with **6** forms the azomethine ylide **14**, which undergoes 1,5-electrocyclisation[9,13] to form **15**. Compound **13** arises from **15** by the opening of the pyran ring, where aromatisation of the pyrrole ring in **13** is the driving force for the opening of the pyran ring (Scheme 3). Steric interaction may be responsible for prohibiting [3 + 2] cycloaddition reaction.

As in our earlier reports,[12,14] the multiplicities of the methylene protons in $^{1}$H NMR spectrum of **13** call for special mention. The methylene protons appear as singlets in compound **13b**, although they appear in compounds **13a** and **c** with their usual multiplicities. We still have no explanation for this unusual observation.

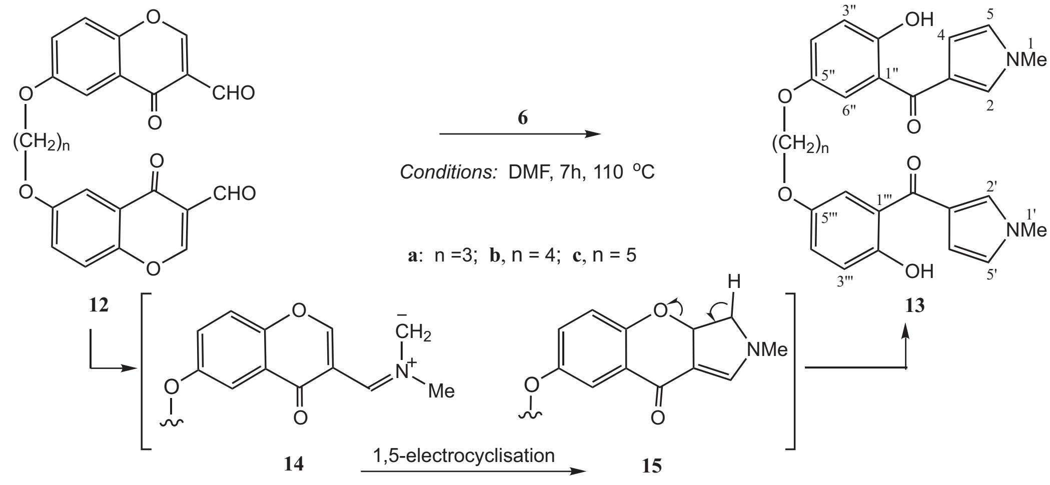
In conclusion: we have reported a synthesis of 2-chromonyl-3-salicyloyl-2,5-dihydropyrrole **10** from **1** by *in situ* generation of azomethine ylide **5**, followed by a [3 + 2] cycloaddition reaction, whereas the corresponding bischromones **12** form the azomethine ylide **14**, which then undergo 1,5-electrocyclisation reaction to produce bis-3-salicyloylpyrroles **13**.

## Experimental

IR spectra were recorded on a Beckman IR 20A in KBr, $^{1}$H NMR spectra in $CDCl_3$ with $SiMe_4$ as internal standard on a Bruker 300 MHz spectrometer, mass spectra on Qtof Micro YA 263 instrument and elemental analyses on Perkin Elmer 240 C elemental analyser. Light petroleum refers to the fraction with distillation range 60–80°C.

*General procedure for the reaction of sarcosine* (**6**) *with chromone-3-carbaldehyde* (**1**) *or di(chromone-3-carbaldehyde)* (**12**)

A mixture of **1** (1 mmol) and **6** (90 mg, 1 mmol) or a mixture of **12** (1 mmol) and **6** (180 mg, 2 mmol) in DMF (5 ml) was heated at



**Scheme 3**

110°C (bath temperature) for 7 h. The reaction mixture was cooled and poured in ice-water (50 g). The deposited solid was filtered, dried and chromatographed over silica gel (100–200). From the reaction mixture of **1**, compounds **9** and **10** were isolated using 10% benzene in light petrol and benzene as eluent, respectively. From the reaction mixture of **12**, compound **13** was obtained using benzene as eluent.

*4H-Chromen-4-one* (**9a**): White crystalline solid (60 mg, 41%); m.p. 58°C (lit.[15] m.p. 56°C).

*6-Methyl-4H-chromen-4-one* (**9b**): White crystalline solid (60 mg, 37%); m.p. 92°C (lit.[15] m.p. 93°C).

*6-Chloro-4H-chromen-4-one* (**9c**): White crystalline solid (75 mg, 42%); m.p. 138°C (lit.[15] m.p. 140°C).

Compounds **9a–c** are identical in all respects to those of authentic samples.

*3-[3-(2-Hydroxybenzoyl)-1-methyl-2,5-dihydropyrrol-2-yl]-4H-chromen-4-one* (**10a**): Yellow crystalline solid (50 mg, 29%), m.p. 190°C. IR: $\nu_{max}$/cm$^{-1}$ 3450, 3010, 2860, 1640, 1630, 1450. $^1$H NMR: δ 3.41 (3 H, s, 1'-$CH_3$), 3.81 (1 H, dd, *J* = 13.0, 6.0 Hz, 5'-H), 4.09 (1 H, m, 5'-H), 5.17–5.20 (1 H, m, 2'-H), 6.87–6.95 (2 H, m, 3"-H and 8-H), 7.02–7.09 (2 H, m, 5"-H and 6-H), 7.42–7.49 (2 H, m, 4"-H and 7-H), 7.55 (1 H, dd, *J* = 7.9, 1.6 Hz, 6"-H), 7.69 (1 H, brs, 2-H), 7.96 (1 H, dd, *J* = 7.8, 1.6 Hz, 5-H), 8.05–8.06 (1 H, m, 4'-H), 11.51 (1 H, s, exchangeable, OH). Anal. calcd. for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03. Found: C, 72.42; H, 4.80; N, 3.98%.

*3-[3-(2-Hydroxy-5-methylbenzoyl)-1-methyl-2,5-dihydropyrrol-2-yl]-6-methyl-4H-chromen-4-one* (**10b**): Yellow crystalline solid (60 mg, 32%), m.p. 208–210°C. IR: $\nu_{max}$/cm$^{-1}$ 3420, 2980, 2900, 1635, 1615, 1460. NMR: $\delta_H$ 2.27 (3 H, s, 5"-$CH_3$), 2.30 (3 H, s, 6-$CH_3$), 3.38 (3 H, s, 1'-$CH_3$), 3.77 (1 H, dd, *J* = 12.3, 6.8 Hz, 5'-H), 4.05 (1 H, dd, *J* = 12.3, 1.3 Hz, 5'-H), 5.11 (1 H, d, *J* = 6.8 Hz, 2'-H), 6.81 (1 H, d, *J* = 8.3 Hz, 3"-H), 6.90 (1 H, d, *J* = 8.3 Hz, 8-H), 7.21–7.28 (3 H, m, 4"-H, 7-H and 6"-H), 7.64 (1 H, s, 2-H), 7.72 (1 H, d, *J* = 1.0 Hz, 5-H), 8.00 (1 H, brs, 4'-H), 11.27 (1 H, s, exchangeable, OH); $\delta_C$ 20.42 ($ArCH_3$), 20.56 ($ArCH_3$), 47.30 (N–$CH_3$), 58.22 (2'-C), 74.54 (5'-C), 107.54 (3-C), 116.82 (3"-C), 117.74 (8-H), 119.71 (1"-C), 121.14 (4a-C), 124.50 (5"-C), 127.21 (5-C), 127.45 (6-C), 131.29 (3'-C), 131.64 (6"-C), 132.24 (4'-C), 135.58 (4"-C), 135.78 (7-C), 155.63 (2-C), 157.00 (8a-C), 159.53 (2"-C), 179.07 (pyran CO), 197.60 (benzoyl CO). MS (positive ion electrospray): *m/z* 398 (M + $Na^+$). Anal. Calcd. for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.39; H, 5.48; N, 3.56%.

*6-Chloro-3-[3-(5-chloro-2-hydroxybenzoyl)-1-methyl-2,5-dihydropyrrol-2-yl]-4H-chromen-4-one* (**10c**): Yellow crystalline solid (75 mg, 36%), m.p. 202–204°C. IR: $\nu_{max}$/cm$^{-1}$ 3470, 3080, 2927, 1647, 1629, 1467. $^1$H NMR: δ 3.42 (3 H, s, 1'-$CH_3$), 3.79 (1 H, dd, *J* = 12.7, 7.0 Hz, 5'-H), 4.10 (1 H, dd, *J* = 12.7, 1.0 Hz, 5'-H), 5.14 (1 H, d, *J* = 7.0 Hz, 2'-H), 6.88 (1 H, d, *J* = 8.6 Hz, 3"-H), 6.97 (1 H, d, *J* = 8.8 Hz, 8-H), 7.36–7.39 (3 H, m, 4"-H, 7-H and 6"-H), 7.66 (1 H, s, 2-H), 7.90 (1 H, d, *J* = 1.4 Hz, 5-H), 8.00 (1 H, brs, 4'-H), 11.28 (1 H, s, exchangeable, OH). Anal. Calcd. for $C_{21}H_{15}Cl_2NO_4$: C, 60.59; H, 3.63; N, 3.36. Found: C, 60.41; H, 3.70; N, 3.25%.

*5",5"'-(Trimethylenedioxy)di-[3-(2-hydroxybenzoyl)-1-methylpyrrole]* (**13a**): Orange-yellow crystalline solid (180 mg, 38%), m.p. 106–108°C. IR: $\nu_{max}$/cm$^{-1}$ 3300, 3110, 2940, 1580, 1525. $^1$H NMR: δ 2.25 (2 H, quintet, *J* = 6.0 Hz, $CH_2$), 3.73 (6 H, s, 2 × N-$CH_3$), 4.15 (4 H, t, *J* = 6.0 Hz, 2 × $OCH_2$), 6.64–6.68 [4 H, m, 2 × (4-H and 5-H)], 6.97 (2 H, d, *J* = 9.0 Hz, 2 × 3"-H), 7.09 (2 H, dd, *J* = 9.0, 3.0 Hz, 2 × 4"-H), 7.29 (2 H, d, *J* = 1.8 Hz, 2 × 2-H), 7.47 (2 H, d, *J* = 3 Hz, 2 × 6"-H), 11.69 (2 H, brs, exchangeable, 2 × OH) Anal. calcd. for $C_{27}H_{26}N_2O_6$: C, 68.34; H, 5.52; N, 5.90. Found: C, 68.50; H, 5.43; N, 5.78%.

*5",5"'-(Tetramethylenedioxy)di-[3-(2-hydroxybenzoyl)-1-methylpyrrole]* (**13b**): Orange-yellow crystalline solid (170 mg, 35%), m.p. 168–170°C. IR: $\nu_{max}$/cm$^{-1}$ 3323, 3122, 2953, 1591, 1527. NMR: $\delta_H$ 1.96 (4 H, s, 2 × $CH_2$),[14] 3.71 (6 H, s, 2 × N-$CH_3$), 4.00 (4 H, s, 2 × $OCH_2$)[14], 6.64 [4 H, brs, 2 × (4-H and 5-H)], 6.94 (2 H, d, *J* = 9.0 Hz, 2 × 3"-H), 7.07 (2 H, dd, *J* = 9.0, 2.2 Hz, 2 × 4"-H), 7.27 (2 H, brs, 2 × 2-H), 7.43 (2 H, d, *J* = 2.2 Hz, 2 × 6"-H), 11.68 (2 H, s, exchangeable, 2 × OH). MS (positive ion electrospray); *m/z* 511 (M + $Na^+$). Anal. Calcd. for $C_{28}H_{28}N_2O_6$: C, 68.84; H, 5.78; N, 5.73. Found: C, 68.70; H, 5.60; N, 5.60%.

*5",5"'-(Pentamethylenedioxy)di-[3-(2-hydroxybenzoyl)-1-methylpyrrole]* (**13c**): Orange-yellow crystalline solid (180 mg, 36%), m.p. 106–108°C. IR: $\nu_{max}$/cm$^{-1}$ 3320, 3130, 2960, 1580, 1520. $^1$H NMR: δ 1.66–1.72 (2 H, m, $CH_2$), 1.82–1.91 (4 H, m, 2 × $CH_2$), 3.75 (6 H, s, 2 × N-$CH_3$), 3.97 (4 H, t, *J* = 6.3 Hz, 2 × $OCH_2$), 6.67–6.69 [4 H, m, 2 × (4-H and 5-H)], 6.97 (2 H, d, *J* = 8.9 Hz, 2 × 3"-H), 7.09 (2 H, dd, *J* = 8.9, 2.9 Hz, 2 × 4"-H), 7.31 (2 H, brs, 2 × 2-H), 7.47 (2 H, d, *J* = 2.9 Hz, 2 × 6"-H), 11.68 (2 H, s, exchangeable, 2 × OH). Anal. Calcd. for $C_{29}H_{30}N_2O_6$: C, 69.31; H, 6.02; N, 5.57. Found: C, 69.21; H, 5.93; N, 5.43%.

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