Chromone studies. Part 14.[1] Unprecedented dimerisation of chromone-3-carbaldehyde-derived Baylis–Hillman adducts

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1,4-Diazabicyclo[2.2.2]octane (DABCO)-catalysed Baylis-Hillman reactions of selected chromone-3-carbaldehydes with methyl acrylate have been shown to afford mixtures of the expected Baylis-Hillman products and unprecedented dimeric derivatives. The Baylis–Hillman products, on heating at 80°C in the presence of DABCO, are converted to the corresponding dimers, the structures of which have been unambiguously established by NMR and X-ray crystallographic analysis. Electron-impact and electrospray MS data for the dimeric systems are discussed.

Keywords: chromone-3-carbaldehyde, Baylis-Hillman reactions

The chromone nucleus is well represented in the structures of natural products, many of which exhibit pharmacological activity. Recently reported examples of such compounds include the anti-inflammatory flavonoids, santin and ermanin, isolated from *Tanacetum microphyllum* by Martinez *et al*.,[2] and the potent cytotoxin, hormothamnione – a 3-methylchromone derivative isolated from the blue-green marine algae, *Cryptophyte chrysophaeum* Taylori, by Gerwick *et al*.[3] Our own interest in chromone systems has been focussed largely on their physical-organic properties, and is illustrated by earlier studies on the influence of remote substituents on the acidity of chromone-2-carboxylic acids,[4] the basicity of 2-(dimethylamino)chromones[5] and the kinetics of dimethylamine-mediated ring opening of chromone-2-carboxamides.[6] A parallel interest has involved the application of Baylis–Hillman methodology[7] in the synthesis of various heterocyclic systems.[8]

In this paper, we report the results of an investigation into the use of chromone-3-carbaldehydes as Baylis–Hillman substrates – an investigation based on the expectation that reaction might also occur at one or more of the available electrophilic centres of the chromone substrate (see Fig. 1), giving rise to some novel chemistry. Chromone-3-carbaldehydes are known to act as selective inhibitors of $p56^{lck}$ tyrosine kinase,[9] and have been shown to serve as versatile synthons in the construction of unusual heterocyclic compounds.[10] Several methods of preparing these systems have been reported.[11] Of these, the Vilsmeier–Haack approach[12] is the most convenient, and was used to prepare the series of chromone-3-carbalde-hydes **2a–f** (Scheme 1) from the corresponding 2-hydroxyacetophenone precursors **1a–f** in yields ranging from 52 to 72%.

The Baylis-Hillman reaction is believed to involve nucleophilic addition of a zwitterionic intermediate (*e.g.* **5**; Scheme 2) to aldehyde substrates. In the case of chromone-3-carbaldehydes, such attack could occur, in principle, at any of the three electrophilic centres illustrated in Fig. 1. In the event, when the chromone-3-carbaldehydes **2a–f** were treated with methyl acrylate in the presence of the tertiary amine catalyst, 1,4-diazabicyclo[2.2.2]octane (DABCO), for 21 days, the corresponding Baylis-Hillman products **3a–f** were isolated, after extensive chromatography, in low yield (8–17%). In most cases, additional products (subsequently identified as the chromone dimers **4a–e**) were obtained in similar yields.

While the Baylis–Hillman products **3a–f** were readily characterized from their high-resolution MS and spectroscopic data, identification of the additional products proved somewhat more difficult. The ^{13}C NMR spectrum of the parent system **4a** indicated the presence of no less than 28 different carbon atoms (including two methyl, two methylene and four carbonyl carbons), while the HRMS data indicated a molecular ion at *m*/z 502.1257 corresponding to the molecular formula, $C_{28}H_{22}O_9$. Single crystal X-ray analysis (Fig. 2) of this compound finally indicated its structure to be as shown for compound **4a** in Scheme 1, *i.e.* that of an asymmetrical dimer containing bicyclic and tricyclic moieties and, seemingly, constituted from two molecules of the Baylis–Hillman product **3a**. Selected bond-lengths and angles are detailed in Table 1.

Bandyopadhyay *et al.*[13] have reported the coupling of chromone-3-carbaldehydes in the presence of various reagents to give bis-chromones, while Wähälä and co-workers[14] have described the synthesis of three unique C–C-bridged bis-isoflavones. To our knowledge, however, the formation of the dimeric products **4a–e** is unprecedented. A tentative

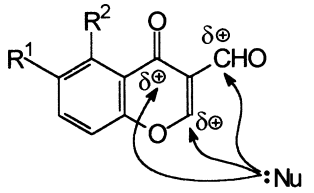
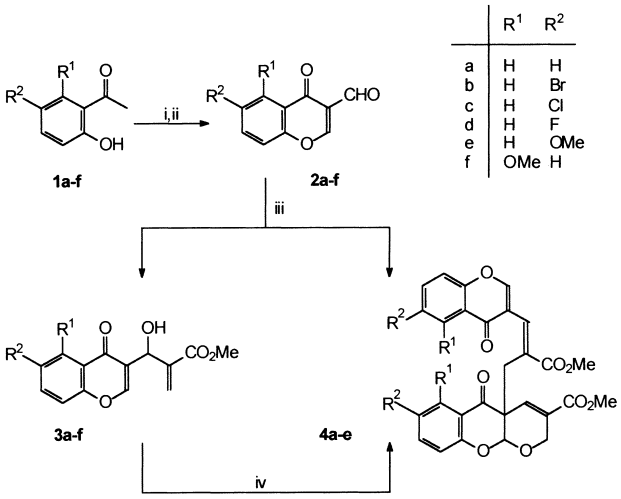


Fig. 1 Electrophilic centres in chromone-3-carbaldehydes.



Scheme 1. *Reagents and conditions.* i, $POCl_3$, DMF; ii, H_2O; iii, $CH_2 = CHCO_2Me$, DABCO, $CHCl_3$, 24h; iv, DABCO, 80°C, 3h.

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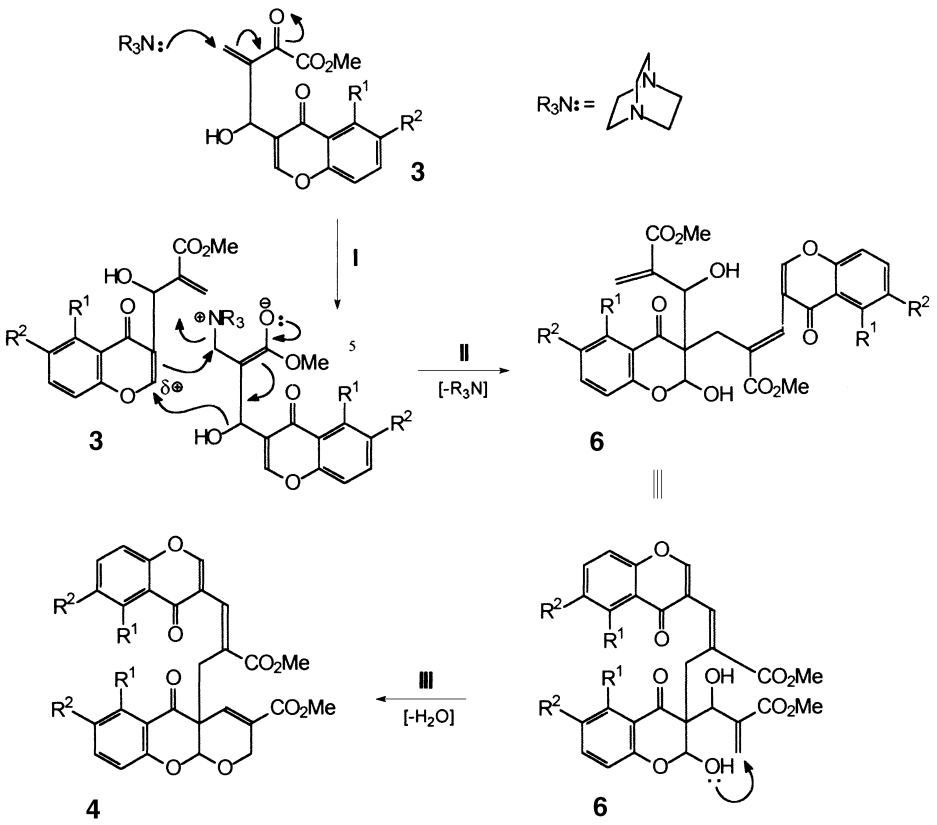

Scheme 2. Proposed dimerisation mechanism (R^1, R^2 as in Scheme 1).

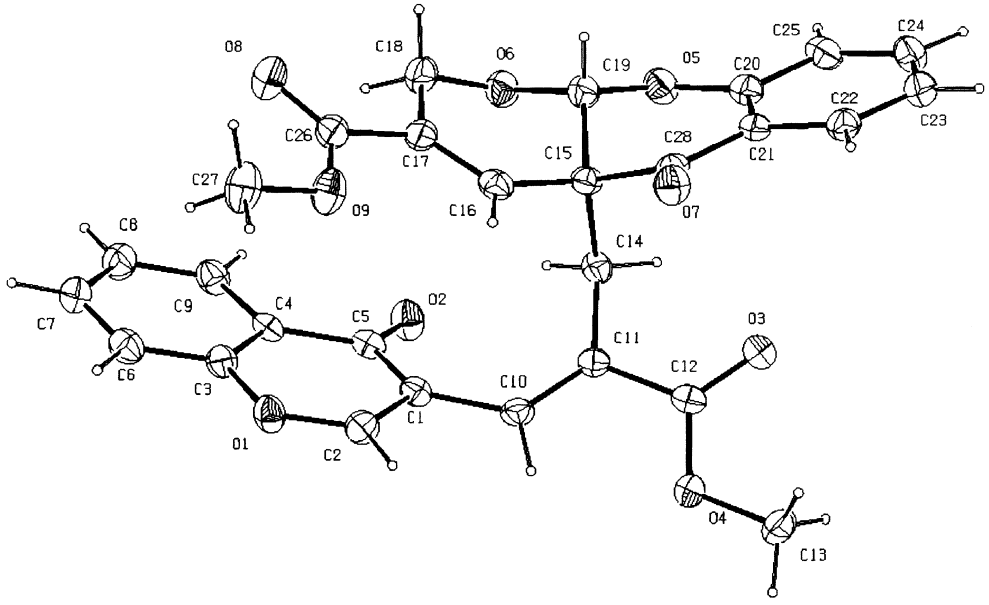

Fig. 2 X-Ray crystal structure of the dimer **4a,** showing the crystallographic numbering.

mechanism, which would account for their generation, is outlined in Scheme 2. In step I, conjugate addition of DABCO to the Baylis–Hillman product **3** affords the nucleophilic zwitterionic enolate **5**, which then engages a second molecule of the chromone derivative **3** (possibly *via* a 6-centred, cyclic transition-state complex involving the α-carbanion, rather than enolate **5,** as the nucleophilic species). Hydroxide ion transfer and nucleophilic displacement of DABCO leads to the dimeric system **6** (Step II). Finally, intramolecular S_N' displacement of hydroxide ion (or conjugate addition-elimination) affords the dimeric product **4** (Step III). The fact that dimerisation of the Baylis–Hillman products **3a–f** can be achieved by heating the monomers (1equiv.) with DABCO (3 equiv.) for 3h at 80°C,[15] provides some support for these proposals. Final conclusions must, however, await the results of a detailed kinetic-mechanistic study.

Major mass spectral fragmentations exhibited by several of the chromone dimers **4** were investigated using a combination of low- and high-resolution electron-impact (EI) MS and electrospray MS^n techniques. Parent → daughter fragmentations,

evident in the electrospray MS^n data for dimer **4a**, have been correlated with significant peaks in the EI spectrum.

In summary, reaction of chromone-3-carbaldehydes under Baylis-Hillman conditions provides access not only to the expected adducts, but also to novel, multifunctional dimeric derivatives, which have considerable potential for synthetic elaboration. Ongoing research will focus on optimising reaction conditions and elucidating the dimerisation mechanism.

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Full text in English

Techniques used: NMR spectroscopy, X-ray crystallography, mass spectrometry

References: 16

Schemes: 3

Figures: 2

Table 1. Bond lengths [Å] and angles {°} for dimer **4a**.

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