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The Directed Lithiation of Some 3-Acylchromone Acetals

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Abstract: 3-Acylchromone acetals are lithiated at C-2. Subsequent electrophilic trapping gives chromones **4** together with a ring-contracted dimer **6**. During the formation of some acetals, an acid-catalysed rearrangement to a 2-substituted 3-formylchromone acetal is observed.

INTRODUCTION

Heteroatom-facilitated metallation has become an increasingly important strategy in organic synthesis and has been of value in the functionalisation of both aromatic and heterocyclic systems.[1] The lithiation of benzopyran derivatives has been previously investigated.[2] It was found that flavones and other chromones in which the 2-position is blocked are lithiated readily [lithium diisopropylamide (LDA) in THF, at -78°C] at C-3 and subsequent reaction with various electrophiles occurs in good yields.[3a,b] Chromones unsubstituted at C-2 are susceptible to ring cleavage by nucleophiles and consequently C-2 lithiation is difficult to achieve. The only reported example concerns the carboxylation of the 6-methyl derivative of **3Aa**; the initial product proved unstable during acidic work-up and a lactone was isolated in very low yield.[3b]

Despite its considerable potential, few examples of directed lithiations of heterocyclic acetals have been reported.[4] We have investigated and optimised the lithiation of the acetals **2**, providing a viable route to functionalised chromones which are useful precursors of heterocycles.

DISCUSSION

3-Formylchromone reacted straightforwardly with the appropriate diol under azeotropic conditions to give acetals **2Aa**, **2Ba**[5] and **2Ca** in high yield.

The ability of the acetal oxygen to co-ordinate the metallating agent combined with the inductive effect of the heteroatom in the pyran ring enhance the acidity of H-2 and facilitate the lithiation of 3-acylchromone acetals **2** at C-2. The red coloured lithio-derivatives **3**, which are stable only at low temperatures, were intercepted by electrophiles, the colour being discharged, to give 2,3-disubstituted chromones **4** (Scheme 1).

The low solubility of the acetal **2Aa** in THF hindered the lithiation and **4Aa** (E = $SiMe_3$) was obtained in low yield when chlorotrimethylsilane was added. Detailed studies have been performed on **2Ba** which is more soluble in THF than the analogous five-membered acetal and in this case the reaction was more

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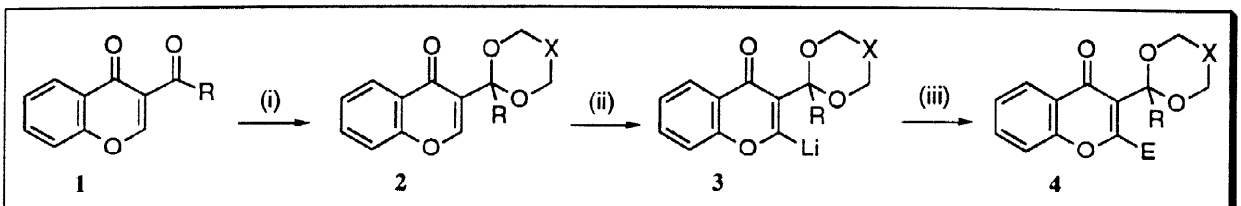
successful. It was essential to use lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF at -78 °C to generate **3**; LDA gave poor yields and intractable products. The anion was quenched with the electrophiles shown in Table 1 to give the compounds **4Ba**.[6] In the ^{1}H NMR spectra of compounds **4Ba**, the absence of a signal for H-2 and upfield shifts of the dioxane methine proton by up to 0.7 ppm are noteworthy.



Reagents: (i) HO-CH_2XCH_2-OH, H^+, PhMe; (ii) LTMP, THF, -78°C; (iii) Electrophile (E^+)

A : X = bond; **B** : X = CH_2; **C** : X = CMe_2; **a** : R = H; **b** : R = Me; **c** : R = Ph.

Scheme 1

In every case, the products **4Ba** were accompanied by a polar compound (TLC) of unknown structure which accounted for up to 40% of the total product. The ^{1}H NMR spectrum of this compound showed the presence of two acetal moieties together with eight aromatic protons, suggesting that it was formed from two molecules of the chromone acetal. This was confirmed by the molecular ion *m/z* 464.1471, corresponding to $C_{26}H_{24}O_8$. The chromone-benzofuran structure **6** was derived by X-ray diffraction (Figure 1).[7]

Table 1: 2-Substituted Chromone Acetals *via* Lithiation and Quenching of **2Ba**

Trapping Reagent	4Ba	
	E	Yield %
$ClCO_2Et$	CO_2Et	56
$ClSiMe_3$	$SiMe_3$	37
p-tolylCHO	*p*-tolylCH(OH)	44
MeCHO	MeCH(OH)	48
EtCHO	EtCH(OH)	40
PhCOCN	PhCO	24

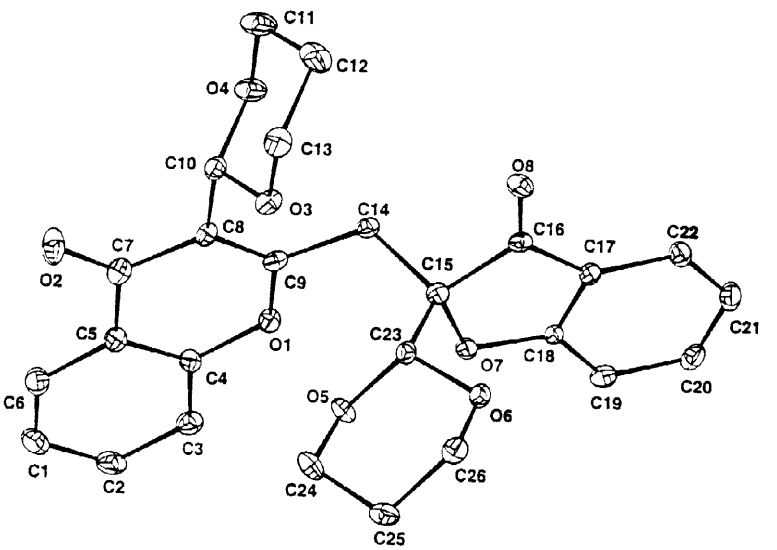
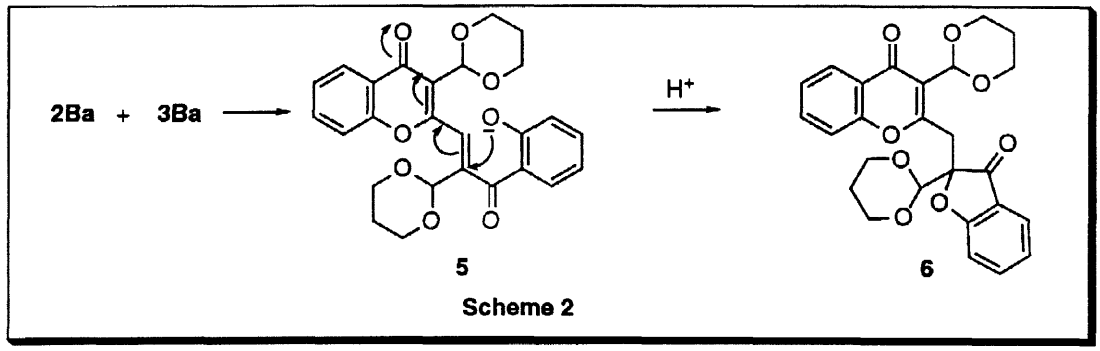


Figure 1: Perspective view and atom labelling of dimer **6**

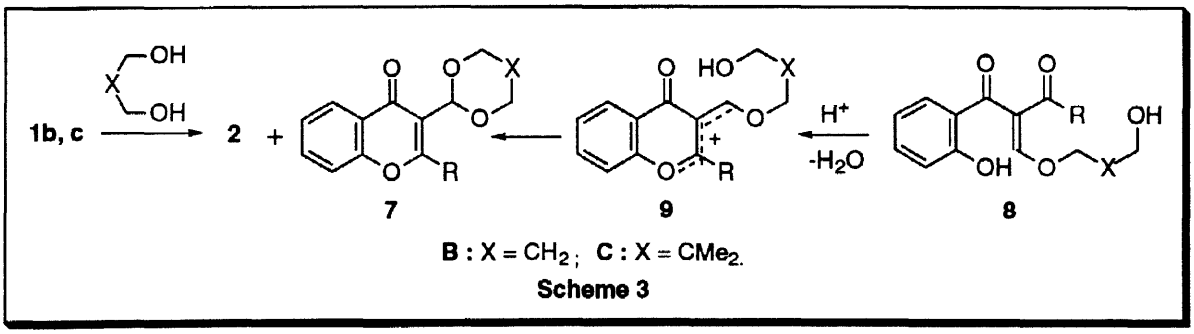
The dimer **6** arises as a result of incomplete metallation of **2**. Michael addition of the lithiochromone **3Ba** to acetal **2Ba** with concomitant ring opening generates the phenoxide ion **5**. Subsequent intramolecular 1,6-conjugate addition effects cyclisation to the product, possibly during work-up, and prototropy of the enol completes the sequence (Scheme 2). Although base-catalysed condensations of chromones are known, the pathways responsible for the formation of **6** are of a different type. Dean observed[8] that treatment of

2,6-dimethylchromone with LDA gave high yields of a methylene-linked chromanone-chromone system, but neither ring-opened nor ring-contracted products were found. The only recorded examples of chromone to benzofuranone ring contractions relate to the reactions of isoflavones with dimethylsulfoxonium methylide[9] and 3-bromochromones with amines.[10] Self-condensation dimers have been obtained from the lithiation of 1-methyl-2-pyridone and 1-methyl-4-pyridone,[11] 1-methyl-4-quinolone[12] and 1-alkylpyrimidin-2(1*H*)-ones.[13]



Scheme 2

The synthesis of other 3-acylchromone acetals and their behaviour towards lithiation were examined. When propan-1,3-diol reacted with **1b** and **1c**, two chromatographically separable compounds **2Bb** and **7Bb** or **2Bc** and **7Bc**, respectively, were formed. With 2,2-dimethylpropan-1,3-diol, **1b** gave **7Cb** exclusively. Formation of these rearranged acetals proceeds by initial addition of the diol to the chromone double bond and ring opening to **8** under the acidic conditions. Bond rotation and cyclisation followed by dehydration give the carbocation **9** which is intercepted by the pendant hydroxy group to give the acetals **7** (Scheme 3). 3-Hydroxymethylenechroman-4-ones rearrange to 3-alkenylchromones *via* a carbocation related to **9**.[14] Although nucleophilic attack at C-2 initiates group migrations in 3-acylchromones,[15] these have never been observed under acetalisation conditions.



B : X = CH_2 ; **C** : X = CMe_2.

Scheme 3

Whilst **2Bb** could be lithiated efficiently and trapped to give **4Bb** [E = *p*-tolylCH(OH)], **2Bc** did not react analogously and the starting material was recovered. Presumably steric demands of the 3-(2-phenyl-1,3-dioxan-2-yl) moiety are responsible for this diminished reactivity.

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6. All new compounds **4** were fully characterised by elemental analyses and their spectra (NMR and IR).
7. Crystal data for **6** ($C_{26}H_{24}O_8$) Mr = 464.45, monoclinic, a = 13.1600(10), b = 10.836(2), c = 16.114(3) Å, β = 108.210(5)°, V = 2182.8(6) Å^3, space group $P2_1/n$, Z = 4, D_c = 1.413 mg m^{-3}, $F(000)$ = 976, μ = 0.105 mm^{-1}, crystal size 0.21 x 0.24 x 0.18 mm, T = 150(2) K, θ = 2.30-24.90°, -14<h<14, -12<k<12, -14<l<18, reflections collected 8891, independent reflections 3331 (full-matrix least-squares on F^2). Atomic co-ordinates thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.
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