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Synthesis of 3-alkenyl-2-arylchromones and 2,3-dialkenylchromones via acid-catalysed retro-Michael ring opening of 3-acylchroman-4-ones

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Abstract—3-Acylchromones and 3-acylflavones, readily available by acylation of 2′-hydroxydibenzoylmethane with acid anhydrides in the presence of base, undergo efficient conjugate reduction with $NaBH_4$ in pyridine to give the corresponding chroman-4-ones/flavanones in high yields. The reduction is both regio- and chemoselective. Treatment of the chroman-4-ones with $MeSO_3H$ generates the 3-alkenyl-2-arylchromones by a dehydrative rearrangement initiated by retro-Michael cleavage of the pyranone ring. This reduction–rearrangement sequence can be extended to 2-alkyl-3-alkenoylchromones to generate 3-alkenyl-2-styrylchromones, the first examples of 2,3-dialkenylchromones.
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Although 2-styrylchromones are well known and easily accessible from 2-methylchromones[1] other alkenylchromones have been much less investigated. 3-Alkenylchromones have been obtained from the reaction of spiro-annulated chroman-4-ones with formamide acetals,[2a] and the acid-catalysed rearrangement of 2-alkyl- and 2,2-dialkyl-3-(hydroxymethylene)chroman-4-ones,[2b] a reaction, which we have extended to the synthesis of 3,4-dihydro-9*H*-xanthen-9-ones[3a] and also to 3-isopropenylthiochromone.[3b]

Reactions of phosphorus ylides with 3-formylchromone provide 3-alkenylchromones. Thus, acylmethylenetriphenylphosphoranes afford the corresponding (*E*) alkenes,[4a] whilst benzylidenetriphenylphosphoranes give, predominantly, the (*Z*)-3-styrylchromones.[4b] However, the reaction with $Ph_2C{=}PPh_3$ is very inefficient,[4c] whilst 3-formylchromones react anomalously in a complex 'Michael–Michael–Wittig' sequence with (2,4-dioxobutylidene)triphenylphosphoranes to give benzophenones.[4d] (*E*)-3-(4-Oxo-1-benzopyran-3-yl)acroleins are available via hydrolysis of the cycloadduct of 3-formylchromone and $H_2C{=}CHOEt$.[5a] Knoevenagel condensation of cyanoacetic and malonic acids with 3-formylchromone provides, respectively, chromone 3-acrylonitrile[5b] and 3-acrylic acid derivatives,[5c] the latter compounds are also accessible from Heck reactions of 3-bromochromones.[5d] Recently, (*E*)-3-styrylchromones have been obtained by the microwave initiated Knoevenagel reaction of phenylacetic acids with 3-formylchromone.[5e] Missing from all these routes is an approach which permits access to simple 3-alkenyl-2-arylchromones. Recently, the acid-catalysed condensation of 2′-hydroxydibenzoylmethanes with phenylacetaldehydes has been reported to provide 3-styrylflavones in a one-pot operation.[6] However, this procedure is limited to arylacetaldehydes and is not amenable to the synthesis of simpler 3-alkenylflavones.

We now report an extension of our earlier work,[2b] which provides an entry to 3-alkenylchromones and flavones from the acid-catalysed retro-Michael ring cleavage of novel, readily available 3-aroyl-2-alkylchroman-4-ones. Application of this dehydrative rearrangement to the hitherto unknown 2-alkyl-3-cinnamoylchroman-4-ones is also described. The requisite starting materials, 2′-hydroxydibenzoylmethanes **1**, are easily available by *O*-acylation of 2′-hydroxyacetophenone followed by Baker–Venkataraman (BV) rearrangement under standard

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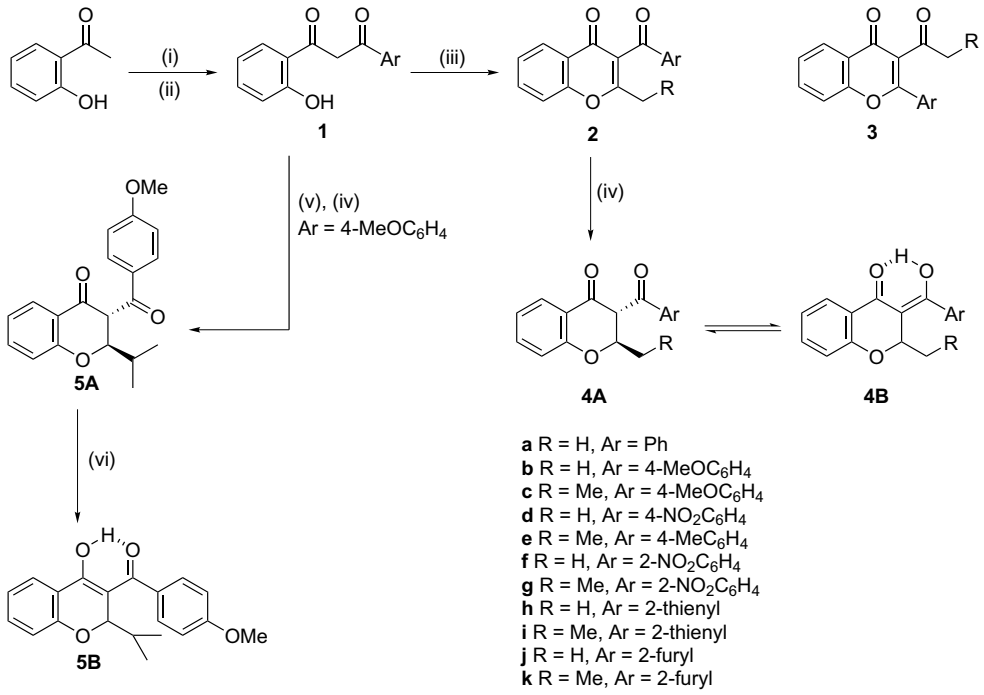
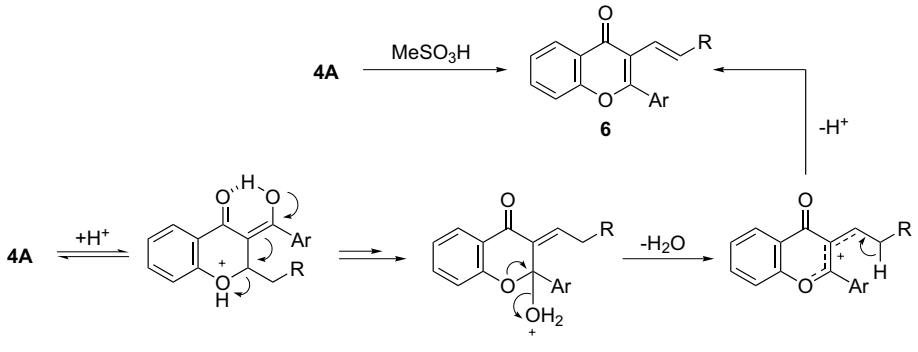


Scheme 1. Reagents and conditions: (i) ArCOCl, pyridine, rt; (ii) KOH, pyridine, rt, then AcOH; (iii) R = H: Ac_2O, NaOAc, Δ; R = Me: $(EtCO)_2O$, Et_3N, Δ; (iv) $NaBH_4$, pyridine, rt, 52–85%; (v) $(Pr^iCO)_2O$, Et_3N, Δ; (vi) $MeSO_3H$, rt.

conditions.[7] Acylation of the 1,3-diketones **1** with either acetic or propionic anhydride gives the 2-alkyl-3-aroylchromones **2** in high yields.[8a–c] None of the isomeric chromones **3** were formed. Smooth and efficient conjugate reduction **2**→**4** was accomplished with $NaBH_4$ in pyridine (Scheme 1).[9] In most cases the 3-acylchroman-4-ones **4** were found to exist exclusively (NMR) as the *trans*-diketo tautomers **4Aa**–**Ae** and **4Ah**–**k**. However, reduction of **2f** and **2g** provided the enol tautomers **4Bf** and **4Bg** as the sole products; evidently conjugation of the *ortho* nitro group with the C-4 carbonyl facilitates intramolecular hydrogen bonding, so favouring the enol tautomer.

The acylation of **1** was also successful with more hindered anhydrides thus **5A** (78%) was obtained from isobutyric anhydride.

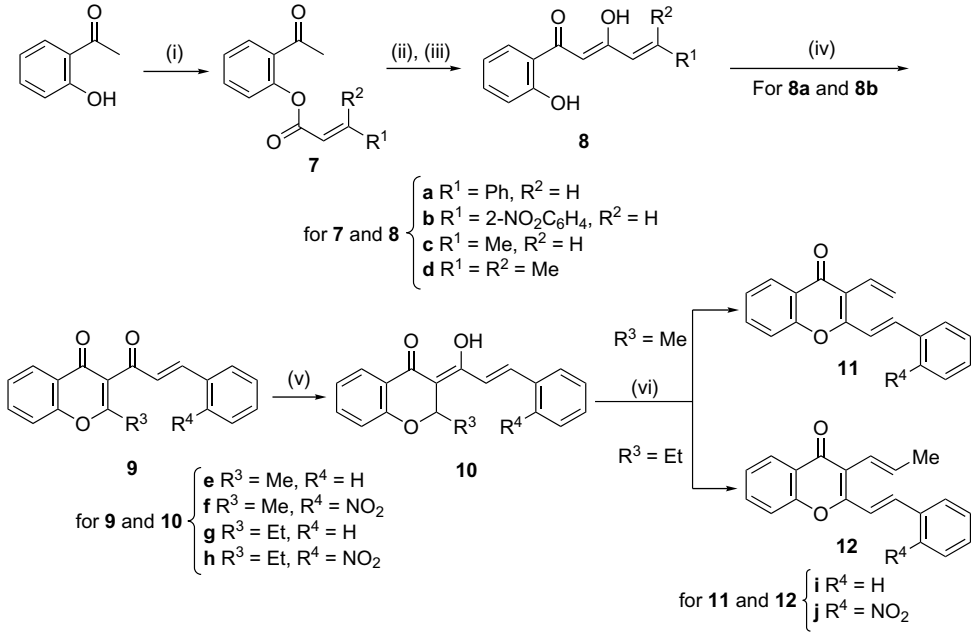
Treatment of chroman-4-ones **4A** with TsOH in hot toluene effected rearrangement to 3-alkenylchromones **6** albeit in low yields. It was found that the conversion **4A**→**6** proceeded more efficiently and in high yield simply by stirring the reactant in neat $MeSO_3H$ at room temperature.[10a] Formation of the alkenylchromone proceeded stereoselectively since chroman-4-ones **4Ac** and **4Ae** provided only **6c** and **6e**.[10b] Interestingly, the furan derivatives **4j**,**k** rearranged to the corresponding alkenylchromones **6j**,**k** without complication. The rearrangement of **4A** to the alkenylchromones **6** occurs via retro-Michael cleavage of the pyranone ring, followed by cyclisation and dehydration. Deprotonation of the intermediate carbocation affords the product (Scheme 2).[11] Surprisingly, attempts to effect rearrangement of the fully enolised diketones **4Bf** and **4Bg**, led only to their complete recovery, even after prolonged reaction times at 75 °C. The steri-



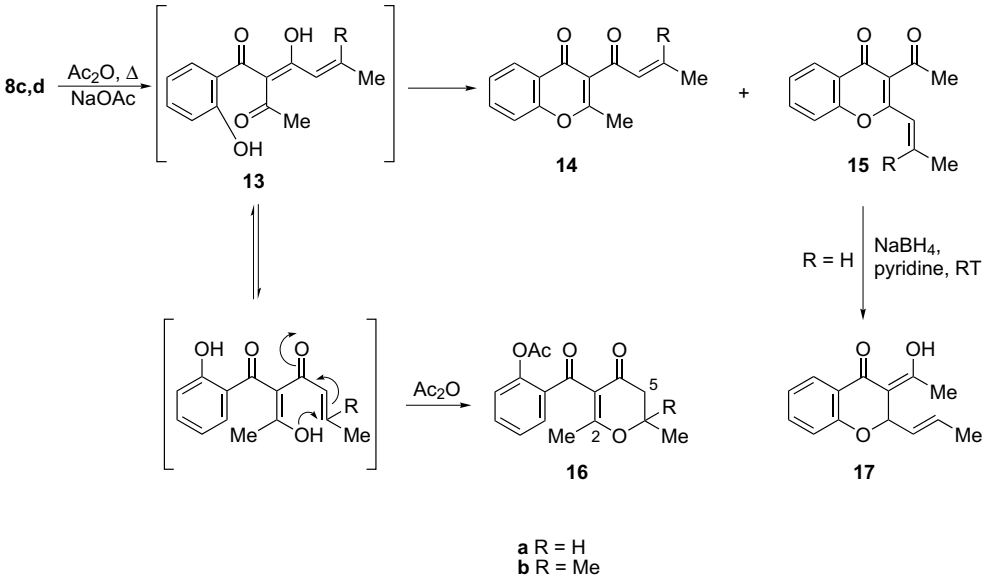
Scheme 2.

cally hindered chromanone **5A** could not be induced to rearrange; exposure to $MeSO_3H$ gave only the enol tautomer **5B** as a stable crystalline product [80%, δ ($CDCl_3$) 16.07 (s, OH), 4.98 (d, J = 3.4 Hz, H-2)].

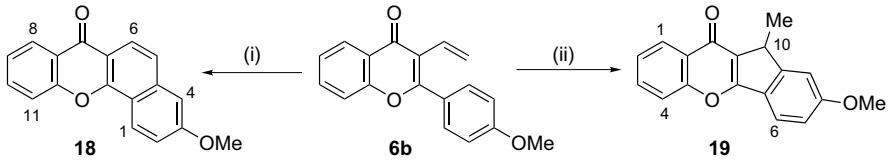
A simple extension of this methodology permits access to 2,3-dialkenylchromones, of which no examples have been reported previously. Thus, the esters **7** were obtained from 2′-hydroxyacetophenone by acylation with alkenoyl chlorides in MeCN under DBU catalysis. We found these conditions to be much more satisfactory than the existing literature procedure.[12a] Aliphatic-BV rearrangement of **7a**–**d** to **8a**–**d** was accomplished by Bu^tOK in THF, following the literature procedure.[12b] Acylation of **8a**,**b** with Ac_2O or $(EtCO)_2O$ effected regiospecific cyclisation to the 3-alkenoylchromones **9e**–**h**. Subsequent reduction with $NaBH_4$–pyridine proceeded in an entirely chemo- and regiospecific manner, with conjugate addition of hydride to the chromone ring, to give **10e**–**h**. When exposed to $MeSO_3H$, the 2-methylchroman-4-ones **10e**,**f** rearranged smoothly to the dialkenylchromones **11i**,**j** (Scheme 3), which were isolated in reasonable yields (48–60%) by simple aqueous work-up and recrystallisation. Rearrangement of the 2-ethylchroman-4-ones **10g**,**h** proceeded to give **12i**,**j** as the only identifiable products (cf. **4Ac**→**6c**).



Scheme 3. Reagents and conditions: (i) $R^1R^2C{=}CHCOCl$, DBU, MeCN, 0 °C; (ii) $KOBu^t$, Bu^tOH, THF, 0 °C; (iii) AcOH; (iv) R^3 = Me: Ac_2O, NaOAc, Δ, 1 h; R^3 = Et: $(EtCO)_2O$, NEt_3, Δ, 1 h; (v) $NaBH_4$, pyridine, rt, 60–72%; (vi) $MeSO_3H$, rt, 1–2 h.



Scheme 4.



Scheme 5. Reagents and conditions: (i) *hv*, PhH, cat. I_2, 36 h; (ii) $BF_3{\cdot}OEt_2$ (6 equiv), $Cl(CH_2)_2Cl$, Δ, 24 h.

Interestingly, acylation of **8c** with Ac_2O provided three new compounds, which could be readily separated and identified as chromones **14a** and **15a** and the pyranone **16a**,[13] in the ratio 1:3:5, respectively. The constitution of **15a** (and hence **14a**) was confirmed by conjugate reduction to **17**. Attempts to effect rearrangement of the latter under a variety of conditions failed to provide a tractable product.

The chromones **14** and **15** are derived from the non-regiospecific cyclisation of the triketone **13** (Scheme 4), whilst **16a** (from **8c**) results from conjugate addition of the enol(ate) to the alkenoyl side chain. Acylation of **8d** similarly provided a mixture of **14b** and **16b** in a 1:1 ratio. We did not observe any of the analogous pyranone **16** (R = Ph, H replaces 6-Me) from reaction of **8a** with Ac_2O; presumably 1,4-addition is retarded because of increased conjugation in this system. No reactions of **8**, which provide 3-acyl-5,6-dihydropyran-4-ones have been reported previously.[14]

The alkenylchromones offer considerable scope for the synthesis of fused systems either by cycloaddition,[3,15] electrocyclisation or electrophilic cyclisation. Examples of the latter two annulation protocols with **6b** are presented in Scheme 5. Thus, photodehydrocyclisation provided the benzo[*c*]xanthone **18**[16a] (70%). Electrophilic cyclisation to the indenopyran **19**[16b] (40%) was initiated with BF_3-etherate, providing an expedient approach to these systems. Surprisingly, compound **6h** failed to react under these conditions. Further studies of the scope and limitations of this reaction are underway.

In summary, a new route to the hitherto difficultly accessible 3-acyl-2-substituted chroman-4-ones is described. Rearrangement of these compounds provides 3-vinyl- and 3-prop-2-enyl-derivatives of flavones, 2-(heteroaryl)chromones and 3-alkenyl-2-styrylchromones. Reactions of the new compounds will be described more fully in due course.

Acknowledgements

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10. (a) Typical procedure: 2-(4-nitrophenyl)-3-vinylchromone **6d**. $NaBH_4$ (1.89 g, 0.05 mol) was added in a single portion to a magnetically stirred solution of 2-methyl-3-(4-nitrobenzoyl)chromone **2d**[8b,c] (15.46 g, 0.05 mol) in pyridine (125 ml). The mixture became red and was allowed to stir until all the $NaBH_4$ had dissolved. After 2 h the mixture was diluted with water, acidified with concd HCl and extracted with EtOAc (3 × 100 ml). The combined extracts were washed with 2 M HCl, water and then dried

(Na_2SO_4) and evaporated to give *trans*-**4Ad** (12.45 g, 80%) as pale yellow crystals from MeOH, mp 164–166 °C. ν_{max} (Nujol)/cm^{-1} 1695, 1665, 1603; δ_H ($CDCl_3$, 250 MHz) 1.50 (3H, d, J = 6.4 Hz, 2-CH_3), 4.60 (1H, d, J = 11.5 Hz, H-3), 5.08 (1H, dq, J = 11.5, 6.4 Hz, H-2) 7.01–8.36 (8H, m, Ar–H). Compound **4Ad** (7.78 g, 0.025 mol) was added to $MeSO_3H$ (40 ml) and the mixture kept at rt until the reaction was complete (ca. 2 h). Following aqueous work-up the product was extracted into EtOAc, to give chromone **6d** (6.95 g, 95%) as an off-white microcrystalline powder mp 147–149 °C from MeOH, ν_{max} (Nujol)/cm^{-1} 1650, 1606. δ_H ($CDCl_3$, 400 MHz) 5.56 (1H, dd, J = 9.6, 4.4 Hz, –CH=C*H*H) 6.34–6.39 (2H, m, CH=CH*H* and C*H*=CH_2), 7.44–7.74 (3H, m, Ar–H), 7.88–7.94 (2H, m, 4-$NO_2C_6H_4$) 8.32 (1H, dd, J = 8.0, 1.6 Hz, H-5), 8.36–8.41 (2H, m, 4-$NO_2C_6H_4$) Other 3-alkenylchromones were prepared similarly. Yields (%) **6a** (70), **6c** (87) **6d** (95), **6e** (62) **6h** (30), **6i** (40), **6j** (66), **6k** (60); (b) Representative spectral data for *trans*-2-(4-methylphenyl)-3-propenylchromone **6e**: δ_H ($CDCl_3$, 400 MHz) 1.79 (3H, dd, J = 6.7, 1.7, Hz, =CHCH_3), 2.45 (3H, s, CH_3), 6.11 (1H, dq, J = 15.7, 1.7 Hz, C*H*=CHCH_3), 6.89 (1H, dq, J = 15.7, 6.7 Hz, CH=C*H*CH_3), 7.30–7.44 (4H, m, Ar–H), 7.58–7.64 (3H, m, Ar–H), 8.27 (1H, dd, J = 8.0, 1.5 Hz, H-5); δ_C 19.76, 21.53, 117.76, 117.86, 121.39, 123.50, 124.75, 126.16, 128.93, 129.51, 130.52, 132.67, 133.19, 140.69, 155.44, 161.88, 177.73; CI-HRMS $[M+H]^+$ found 277.1223, $C_{19}H_{16}O_2+H^+$ requires 277.1221.

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14. The only reported example of direct formation of a pyranone ring from 1,3-diketones **8** concerns the cycloaddition of pyrrolidinocycloalkenes to (*E*)-1-(2-hydroxyphenyl)-5-phenylpent-4-ene-1,3-dione **8a**, which provides cycloalkeno[*a*]- and cycloalkeno[*d*]xanthones, Letcher, R. M.; Yue, T.-Y.; Chiu, K.-F.; Kelkar, A. S.; Cheung, K.-K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3267–3276.
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