COMMUNICATION

Application of Baylis–Hillman methodology in a chemoselective synthesis of 3-acyl-2*H*-1-chromenes

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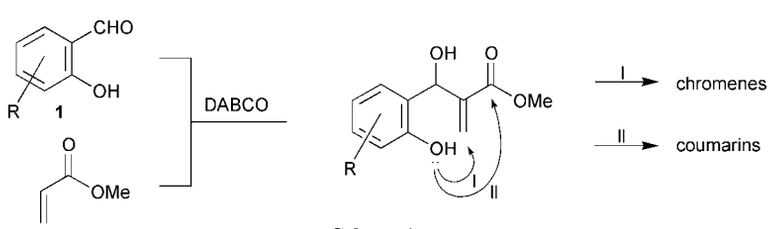
Received (in Cambridge, UK) 10th February 2000, Accepted 9th March 2000
Published on the Web 10th April 2000

Reaction of 2-hydroxybenzaldehydes with alkyl vinyl ketones in the presence of 1,4-diazabicyclo[2.2.2]octane proceeds with regioselective cyclisation to afford the corresponding 2*H*-1-chromenes in yields of up to 87%.

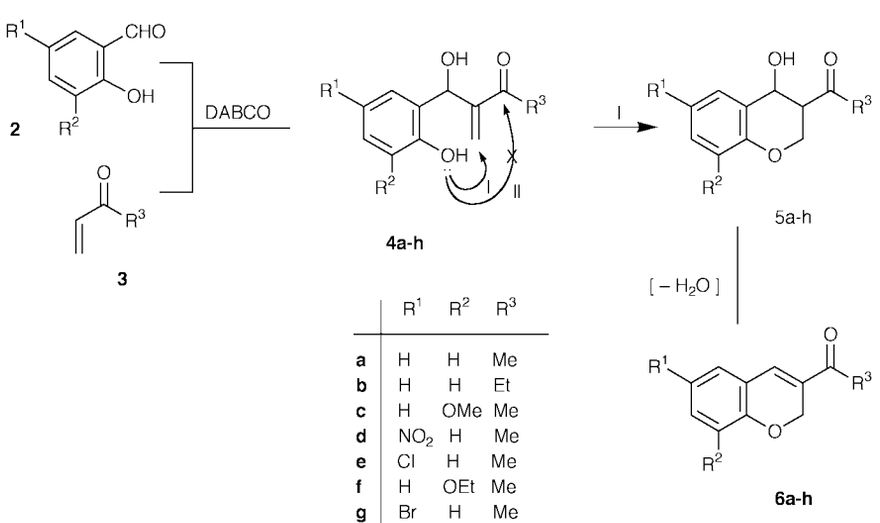
The 2*H*-1-chromene system is widely distributed in nature,[1] and some derivatives have been shown to exhibit pharmacological activity.[2] The synthesis of 2*H*-1-chromenes *via* the cyclisation of suitably elaborated phenyl ethers commonly suffers from a lack of regiocontrol in the cyclisation step and, while this particular problem may be obviated by the use of *o*-hydroxybenzaldehydes (to establish the ring-fusion positions), construction of the requisite acyclic precursors may involve several steps and elevated temperatures may be necessary to achieve cyclisation.[1] New methods for preparing 2*H*-1-chromenes continue to be reported.[3]

The Baylis–Hillman reaction[4] has been shown to provide convenient access to benzannulated heterocyclic systems,[5] and we have recently described a novel synthesis of quinoline derivatives *via* the regioselective, reductive cyclisation of Baylis–Hillman products of *o*-nitrobenzaldehydes.[6] However, our earlier attempts to obtain 2*H*-1-chromenes by the analogous cyclisation of *o*-hydroxybenzaldehyde derivatives **1** afforded complex mixtures of coumarins and chromenes (Scheme 1).[7] In fact, representative examples of no less than eight classes of coumarin and chromene derivatives were obtained from reactions of salicylaldehydes with methyl acrylate, the non-regioselective cyclisation of the putative Baylis–Hillman products **1** being considered pivotal to their formation. Although the 2*H*-1-chromenes were the most common products isolated in this early investigation, low yields and the complexity of the product mixtures rendered this approach synthetically impractical. These short-comings have been addressed by careful optimisation of reaction conditions and the use of alkyl vinyl ketones as the activated alkene component, enabling us, now, to report an efficient and remarkably chemoselective synthesis of 3-substituted 2*H*-1-chromenes.

While conjugate addition of the phenolic oxygen to the α,β-unsaturated carbonyl system (Path I, Scheme 1) leads to chromenes, competitive cyclisation, involving attack at the acyl carbon of the ester moiety, affords the coumarin analogues (Path II). Since the latter cyclisation mode involves acyl substitution, it was expected that replacement of the *O*-alkyl group with a poor leaving group might inhibit substitution and favour conjugate addition. Consequently, salicylaldehyde **2** ($R^1 = R^2 = H$; Scheme 2) was reacted with methyl vinyl ketone (MVK) **3** ($R^3 = Me$) in the presence of 1,4-diazabicyclo[2.2.2]-



Scheme 1



	R^1	R^2	R^3
a	H	H	Me
b	H	H	Et
c	H	OMe	Me
d	NO_2	H	Me
e	Cl	H	Me
f	H	OEt	Me
g	Br	H	Me
h	Br	Br	Me

Scheme 2

DOI: 10.1039/b001148g

Table 1 Data for the formation of 2*H*-1-chromene derivatives **6a**–**h**

Entry	Compd.	R^1	R^2	R^3	Yield[a] (%)	Mp/°C
1	**6a**	H	H	Me	81	39–40
2	**6b**	H	H	Et	83	—[b]
3	**6c**	H	OMe	Me	79	100–101
4	**6d**	NO_2	H	Me	54	132–134
5	**6e**	Cl	H	Me	56	47–48
6	**6f**	H	OEt	Me	84	68–70
7	**6g**	Br	H	Me	87	59–60
8	**6h**	Br	Br	Me	29 (82)[c]	74–75

[a] Chromatographed material. [b] Oil. [c] Together with the 4-hydroxychromane **5h** (53%), mp 132–134 °C.

octane (DABCO), as catalyst, and chloroform, as solvent and, indeed, the reaction proceeded with regioselective cyclisation to afford the desired 2*H*-1-chromene **6a**, albeit with relatively low conversion (*ca*. 40%) (Scheme 2). Since replacement of the methoxy group by methyl was clearly inhibiting acyl substitution (Path II), attention was turned to optimising the yield. Variations of the catalyst concentration and the solvent system (*N*,*N*-dimethylformamide, ethylene glycol, tetrahydrofuran, and water) were examined, the best result (66% conversion) being obtained using 0.8 equivalents of DABCO and a vigorously stirred heterogeneous mixture of chloroform and water as the solvent system. Finally, the progress of the reaction was monitored by ^{1}H NMR spectroscopy, and additional MVK and DABCO were added, at intervals, when the reaction rate was observed to decrease significantly. Under these conditions the desired 2*H*-1-chromene **6a** was obtained in 81% yield.

This protocol was successfully extended to other substrates, the corresponding products **6b**–**6g** being isolated in yields ranging from 54 to 87% (Table 1). In the reaction of the dibromo system **2h**, however, the spontaneous dehydration step (**5**→**6**) was incomplete, and the 4-hydroxychromane **5h** (53%) was isolated together with the chromene **6h** (29%)—an observation which supports the conjugate addition–elimination sequence outlined in Scheme 2. A number of other activated alkenes **3** (R^3 = H; CN; SO_2Ph; SO_3Ph) have similarly been found to favour cyclisation *via* conjugate addition with the formation of the corresponding 3-substituted 2*H*-1-chromenes.[8] In the case of phenyl vinyl ketone (R^3 = Ph), however, dimerisation[9] of the alkene proved dominant and the expected chromene was only obtained in 10% yield; these results will be reported more fully in due course. René and Royer[10] have also prepared substituted chromenes by reacting *o*-hydroxybenzaldehydes with acrylate derivatives in the presence of base; in their case, however, the condensation is presumably *initiated* by conjugate addition of phenoxide ion to the α,β-unsaturated carbonyl moiety.

In summary, the Baylis–Hillman reaction of *o*-hydroxybenzaldehydes with *alkyl* vinyl ketones constitutes an efficient, convenient and highly chemoselective route to 3-acyl-2*H*-1-chromenes—products with obvious potential for elaboration to 3-substituted derivatives.

Experimental

In a typical reaction, a mixture of salicylaldehyde **2** (R^1 = R^2 = H; 1.0 mL, 9.6 mmol), MVK **3** (R^3 = Me; 1.2 mL, 14.4 mmol) and DABCO (0.86 g, 7.68 mmol) in $CHCl_3$ (1 mL) and H_2O (1 mL) was stirred vigorously under N_2 in a stoppered flask at room temperature. After stirring for 24 h, additional MVK (0.4 mL, 4.8 mmol) and DABCO (0.29 g, 2.6 mmol) were added and stirring continued for 72 h before adding further quantities of MVK (0.2 mL, 2.4 mmol) and DABCO (0.1 g, 0.85 mmol) and stirring for a further 72 h. The solvents were then evaporated and the solid residue chromatographed [flash chromatography on silica; elution with hexane–EtOAc (4:1)] to give **6a** (1.35 g, 81%).

Compounds **6b**, **6d**, **6e** and **6h**, which appear to be new, and the known chromene derivatives,[11] **6a**, **6c**, **6f** and **6g**, were characterised by elemental (high resolution MS) and ^{1}H and ^{13}C NMR spectroscopic analyses.

Acknowledgements

We thank the National Research Foundation (NRF) for a bursary (to X. W. N.) and Rhodes University and the NRF for generous financial support.

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