Regioselective Preparation of 6-Allyl-7-hydroxycoumarin from 7-Allyloxycoumarin *via* Boron Halide catalysed *ortho*-Claisen Rearrangement of 4'-Allyloxycoumaric Acid Derivatives

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An efficient synthesis of 6-allyl-7-hydroxycoumarin, a key intermediate for the preparation of linear coumarins, is described *via* a regioselective catalysed *ortho*-Claisen rearrangement of methyl 4'-allyloxy-2'-methoxycinnamate.

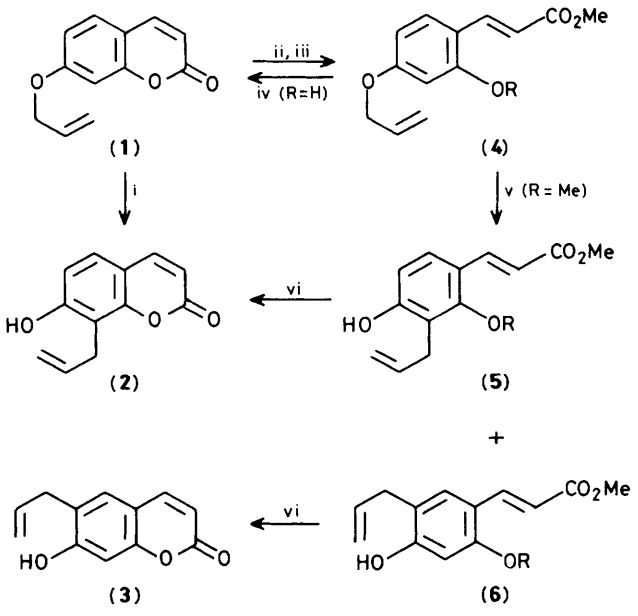
Coumarins which are oxygenated at C-7 and alkylated at either C-6 (linear) or C-8 (angular) are frequent constituents of higher plants, particularly Umbelliferae, and are represented by a wide range of furanocoumarins, pyranocoumarins, and simple alkylated derivatives.[1]

Access to the angular series is possible *via ortho*-Claisen rearrangement of 7-allyloxycoumarins which undergo highly selective rearrangement of the 8-allylated products [*e.g.* (**1**) to (**2**)][2] (Scheme 1). Preparation of the linear isomers by a similar sequence necessitates either reduction of the 3,4-double bond (linear : angular ~1 : 1)[3] or blocking of C-8.[4] Direct substitution of 7-hydroxycoumarins by Lewis acid catalysed reaction with tertiary allylic alcohols likewise furnishes mixtures of 6- and 8-allylated products in low yield.[5]

In earlier work we demonstrated that the trifluoroacetic acid catalysed Claisen rearrangement[6] of methyl 4-allyloxy-2-hydroxybenzoate occurred selectively towards the 5-position.[7] We thus reasoned that disruption of the coumarin nucleus to form the vinylogous coumaric acid derivatives (**4**), should permit similar selective rearrangement to products (**6**) and furnish the desired linear coumarin (**3**) on relactonisation.[8]

Methyl esters (**4a**), (**4b**) were obtained efficiently by treatment of 7-allyloxycoumarin (**1**) with sodium methoxide in methanol at reflux with rigorous exclusion of moisture (traces of hydroxide inhibit cleavage) followed by quenching of the cooled reaction with water [(**4a**), 96%] or acetic anhydride [(**4b**), 76%]. The esters (**4c**), (**4d**) were obtained by alkylation of (**4a**) with methyl iodide or benzyl bromide, K_2CO_3, acetone at reflux [(**4c**), 96%, (**4d**), 92%]. Higher overall yields of (**4c**) and (**4d**) were obtained by this two step procedure than by direct addition of halide to the reaction mixture obtained on cleavage. The olefinic protons of (**4a—d**) appeared as 16 Hz doublets indicating (*E*)-double bond geometry† (Scheme 1).

Thermal rearrangement of (**4a**) and (**4b**) furnished angular coumarin (**2**) [accompanied by some of the acetylated derivative in the case of (**4b**)] as the major product owing to relactonisation occurring before rearrangement; whereas thermal rearrangement of the methyl ether (**4c**) resulted in the formation of (**5c**) and (**6c**) in which the desired regioisomer was the major product [(**5c**) : (**6c**), 1.0 : 2.5]. Attempted improvement of this ratio by use of trifluoroacetic acid catalysis caused total decomposition. In search of milder conditions BCl_3, previously reported to catalyse Claisen rearrangements at low temperatures,[9] was investigated. Conditions could not be found to effect rearrangement without decomposition or relactonisation of (**4a**) and the acetate (**4b**) was found to be readily converted initially into (**4a**). Gratifyingly, treatment of (**4c**) with an excess of BCl_3 (3 equiv., CH_2Cl_2, −50 °C, 1 h, −20 °C, 2 h) cleanly furnished the linear isomer (**6c**) contaminated with less than 10% (**5c**) by n.m.r.



a; R = H
b; R = Ac
c; R = Me
d; R = $PhCH_2$

Scheme 1. *Reagents:* i, 220 °C; ii, NaOMe, MeOH, reflux; iii, H_2O (**4a**), Ac_2O (**4b**), MeI, K_2CO_3, acetone, reflux (**4c**), $PhCH_2Br$, K_2CO_3, acetone , reflux (**4d**); iv, 180 °C; v, BCl_3 (3 equiv.), CH_2Cl_2, −50 → −20 °C; vi, BBr_3 (3 equiv.), CH_2Cl_2, room temp.

analysis. In the adopted procedure however, the mixture was not isolated, but treated directly with BBr_3 (3 equiv., room temp.) to effect demethylation and concomitant relactonisation. The mixture of (**2**) and (**3**) (g.c. ratio 1.0 : 10.5) thus obtained was separated by dry column flash chromatography[10] giving 6-allyl-7-hydroxycoumarin (**3**) (78% yield) together with the 8-allyl regioisomer (**2**) (8%). In the n.m.r. spectrum of (**3**) the aromatic protons appeared as singlets at δ 7.08 and 7.22 indicating their *para* relationship. Attempts to bias the regiocontrol further, utilising the greater steric bulk of the benzyl group of (**4d**), were again thwarted by facile debenzylation to (**4a**) with BCl_3.

In practice, conversion of 7-allyloxycoumarin (**1**) into pure 6-allyl-7-hydroxycoumarin (**3**), *via* the methyl ether (**4c**), can be carried out in 70% overall yield on a preparatively useful scale without separation of intermediates. A single recrystallisation is sufficient to furnish the desired product uncontaminated by its angular isomer (EtOAc–hexane, m.p. 145—148 °C, lit.,[4] 149 °C).

This procedure complements the existing Claisen rearrangement approach to angular coumarin derivatives, and

† All novel compounds isolated gave spectroscopic and microanalytical data in accord with their assigned structures.

permits the efficient preparation of 6-allyl-7-hydroxycoumarin (**3**), an important precursor to linear coumarins such as the furanocoumarin psoralen.[4] We will report further applications of this procedure in due course.

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