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# A NEW AND EFFICIENT ROUTE TO 3-(1,1-DIMETHYLALLYL)COUMARINS

Isidro G. Collado, Rosario Hernández-Galán, Guillermo M. Massanet, Francisco Rodríguez-Luis and Javier Salvá

Departamento de Química Orgánica. Facultad de Ciencias. Universidad de Cádiz. Apdo. 40, 11510 Puerto Real, Cádiz, SPAIN.

*Key Words:* coumarins; 3-(1,1-dimethylallyl)coumarins; angustifolin; Ireland-Claisen rearrangement; Pd promoted sigmatropic rearrangement

***Abstract:*** A new method for the synthesis of 3-(1,1-dimethylallyl)coumarins is described. The key step involves an Ireland-Claisen rearrangement of an allyl ester.

It has been reported that coumarins bearing a 1,1-dimethylallyl moiety at C-3 possess a wide range of biological activities.[1] Studies on the relationship between structure and cytostatic activity strongly suggest that the side chain is an important requirement.[2]

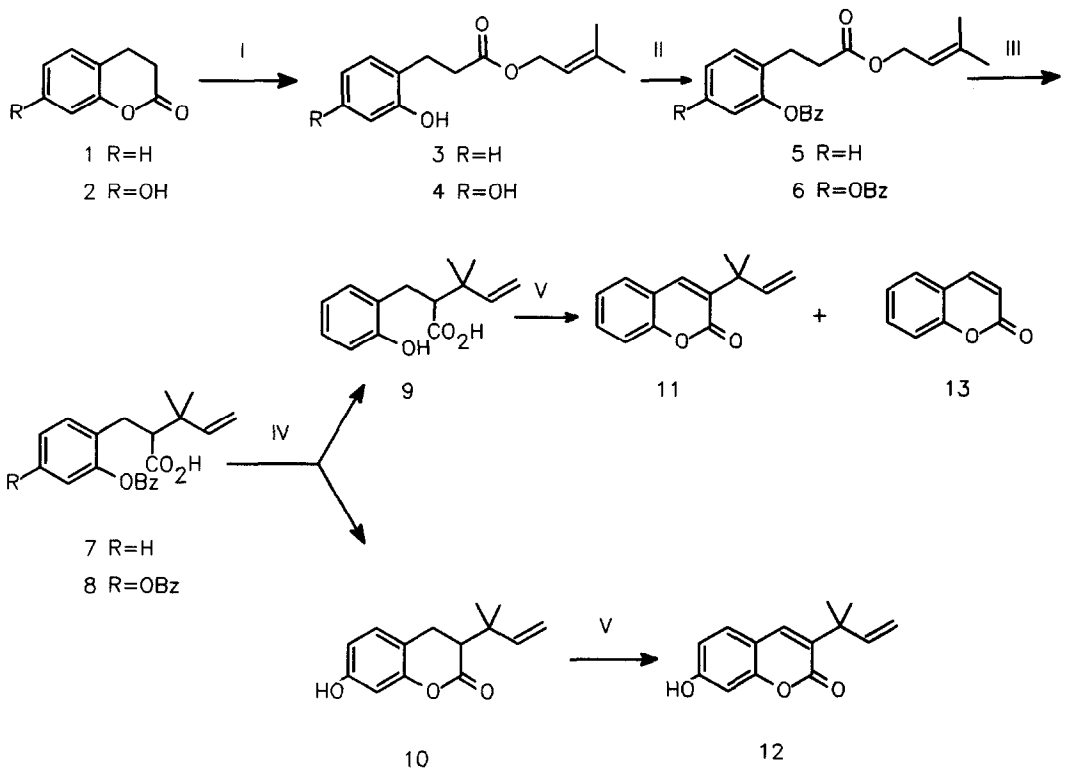
As these compounds are obtained from natural sources, mainly *Rutaceae* plants, in small amounts we have had a continued interest in their synthesis. The key step of our earlier approach involved sigmatropic rearrangements of dimethylallyl ethers of 7-hydroxycoumarin.[3] However this procedure leads to C-3 alkylated coumarins in low yields.

Continuing our efforts towards the synthesis of this type of compound we have attempted the alkylation at C-3 through a different strategy, the key step of which involves an Ireland-Claisen rearrangement of an allyl ester, and leads to a dramatic improvement in yields.

The syntheses have been carried out starting from two different substrates: 3,4-dihydrocoumarin (1) and 3,4-dihydro-7-hydroxycoumarin (2) and are outlined in scheme 1. Dihydroderivative 2 was obtained by catalytic hydrogenation on Pd-charcoal/AcOH of 7-hydroxycoumarin (quantitative yield).

The esters 3 and 4 were obtained, after investigating a range of conditions, by treatment of dihydroderivatives 1 and 2 with sodium 3-methyl-2-butenoxide prepared by addition of sodium to an excess of 3-methyl-2-buten-1-ol (85%, 88%). These reactions proceed with δ-lactone ring opening.

It is well known that esters of allylic alcohols can be rearranged to γ,δ-unsaturated carboxylic acids via the *O*-trimethylsilyl ethers of the ester enolate and such reactions have been extensively studied




I) 3-methyl-2-buten-1-ol,Na/acetone; II) BzBr,$K_2CO_3$/acetone; III) LDA/THF,$Me_3SiCl$
IV) $BBr_3$,$CH_2Cl_2$/-22°C → r.t.; V) $Ph_2O$,reflux,Pd-charcoal

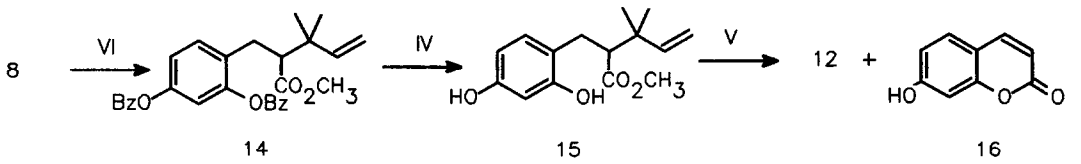
**Scheme 1**

by Ireland.[4] This reaction performed on the esters **3** and **4** might lead to acids appropriately functionalized at C-3. Although attempts to achieve the Ireland-Claisen rearrangement on the phenols **3** and **4** were unsuccessful, the reaction could be carried out when the hydroxyl groups had been previously protected. Thus, treatment of **3** and **4** with benzyl bromide and $K_2CO_3$/acetone lead to the corresponding benzyloxy derivatives **5*** and **6*** (91%, 84%). The rearrangement of **5** and **6** lead to the acids **7*** and **8*** (97%, 92%).[5]

Treatment of **7** and **8** with $BBr_3$ in $CH_2Cl_2$ at -22°C for 1 h and subsequently 1h at room temperature leads to the phenols **9** and **10** (88%,91%).[6] The ring closure in **10** could be explained considering the greater nucleophilicity of the 1,3-dihydroxy intermediate, obtained in the work up, with

respect to the monohydroxy derivative **9**.

In order to obtain the desired 3-(1,1-dimethylallyl)coumarin derivatives, compounds **9** and **10** were refluxed in diphenyl ether with Pd-charcoal yielding coumarins **11** and **12** respectively (25 and 76%). It is worth noting that this latter reaction for **9** afforded in addition to **11**, coumarin **13** (70%) This fact might be explained by a Pd promoted sigmatropic rearrangement followed by lactonization. Pd catalyzed [3.3]-sigmatropic rearrangements have been widely reported[7] and they are a plausible explanation for the formation of C-3 unsubstituted coumarins from the corresponding coumarinic acid derivatives. This result was also observed when the corresponding methyl ester derivative **15** was heated under the same conditions to afford **12** (25%) together with 7-hydroxycoumarin (**16**) (50%) (Scheme 2).




VI) $(Me)_2SO_4$,NaOH/acetone; IV) $BBr_3$,$CH_2Cl_2$/-22°C; V) $Ph_2O$,reflux,Pd-charcoal

**Scheme 2**

The synthesis above described is an excellent method to obtain 3-(1,1-dimethylallyl)-7-hydroxycoumarin (angustifolin)(**12**).[8] This compound, a key precursor for the preparation of many 3-(1,1-dimethylallyl)coumarins has been previously synthesized in 15% overall yield;[3] whereas this new route starting from the same material involves easier separations and leads to an 47% overall yield.

## ACKNOWLEDGEMENTS

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5. To a solution of 0.8 mmol of LDA in 10 ml of THF at -95°C (acetone/$N_2$) 0.4 mmol of benzyl ester were added. The reaction mixture was stirred for 1h at -95°C and then 0.5 mmol of $Me_3SiCl$ were added. After stirring for 1h at -95°C the mixture was allowed to warm up to 25°C and stirred for 12h. The solution was poured into 75 ml of 5% aqueous NaOH and stirred for 10 min. The aqueous layer was washed with ether. The aqueous phase was acidified with concentrated HCl at 0°C and extracted repeatedly with $CH_2Cl_2$. The combined extracts were dried over $Na_2SO_4$ and concentrated.

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• All compounds had satisfactory spectroscopic data. Selected $^1H$ NMR data are the following: **5** ($DCCl_3$) 7.48-6.83(m); 5.29(mt,J=7.3 and 1.4); 5.08(s); 4.54(d,J=7.3); 3.00(dd,J=7.4 and 7.9), 2.64(dd,J=7.9 and 7.4); 1.74(s); 1.67(s). **6** ($DCCl_3$) 7.39-7.25(m); 7.01(d,J=8.2); 6.52(d,J=2.5); 6.44(dd,J=8.2 and 2.5); 5.25(qt,J=7.1 and 1.4); 4.99(s); 4.95(s); 4.50(d,J=7.1); 2.91(d,J=7.1); 2.87(d,J=8.0); 2.58(d,J=8.0); 2.54(d,J=7.1); 1.70(s); 1.63(s). **7** ($DCCl_3$) 7.44-6.79(m); 5.75(dd,J=17.4 and 10.7); 5.02(s); 4.94(dd,J=17.4 and 1.3); 4.88(dd,J=10.7 and 1.3); 2.98(d,J=10.2); 2.65(s); 2.63(d,J=10.2); 1.06(s); 1.02(s). **8** ($CDCl_3$) 7.34-7.20(m); 6.93(d,J=8.0); 6.51(d,J=2.3); 6.37(dd,J=8.0 and 2.3); 5.70(dd,J=17.4 and 10,7); 4.92(s); 4.90(d,J=17.4); 4.84(d,J=10.7); 2.88(d,J=9.6); 2.57(s); 2.56(d,J=9.6); 1.02(s); 0.98(s).

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