A new protocol for the syntheses of (*E*)-3-benzylidenechroman-4-ones: a simple synthesis of the methyl ether of bonducellin

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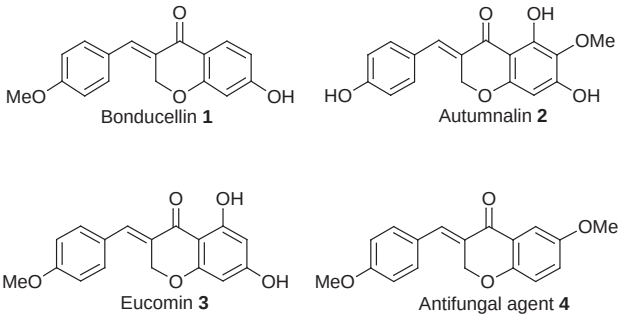
Development of a simple new methodology for the synthesis of (*E*)-3-benzylidenechroman-4-ones using methyl 3-aryl-3-hydroxy-2-methylenepropanoates, the Baylis–Hillman adducts derived from methyl acrylate, and the application of this methodology for the synthesis of the methyl ether of bonducellin, an important natural product, and 3-(4-methoxybenzylidene)-6-methoxychroman-4-one, an antifungal agent, are described.

The (*E*)-3-benzylidenechroman-4-one moiety occupies a special place in the field of heterocycles as this skeleton is an integral part of many natural products and biologically active

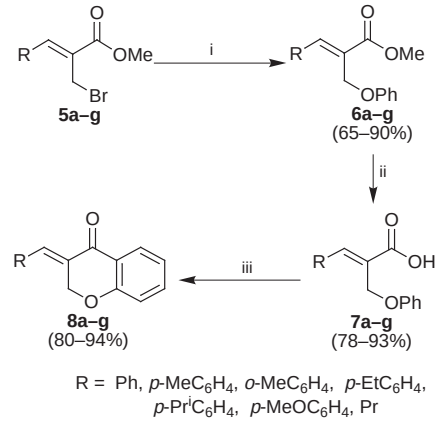


molecules. For example, bonducellin **1** is an important natural product occurring in *Caesalpinia bonducella*[1] and *Caesalpinia pulcherrima*.[2] Autumnalin **2**[3] and Eucomin **3**[4] are interesting naturally occurring molecules present respectively in *Eucomis autumnalis* GRAEB (Liliaceae) and *Eucomis bicolor* BAK (Liliaceae). (*E*)-3-(4-Methoxybenzylidene)-6-methoxychroman-4-one **4** is an antifungal agent.[5] Therefore the development of simple, general and new protocols for the synthesis of the (*E*)-3-benzylidenechroman-4-one skeleton is of considerable importance today in synthetic organic chemistry.

The classical and most of the literature methods for the synthesis of (*E*)-3-benzylidenechroman-4-ones involve the initial synthesis of the chroman-4-one skeleton, followed by the construction of the benzylidene moiety *via* acid or base catalyzed aldol condensation with aryl aldehydes.[6–8] However, to the best of our knowledge, there is no report in the literature of the synthesis of (*E*)-3-benzylidenechroman-4-one involving the initial preparation of the benzylidene moiety and then the construction of the chroman-4-one ring system. We herein disclose the first such methodology, thus developing a new protocol for the synthesis of (*E*)-3-benzylidenechroman-4-ones using methyl 3-aryl-3-hydroxy-2-methylenepropanoates, the Baylis–Hillman adducts derived from methyl acrylate.

The Baylis–Hillman reaction[9–13] has attracted the attention of organic chemists in recent years as this reaction provides synthetically useful multifunctional molecules which have been successfully employed in various stereoselective processes. In continuation of our interest in the Baylis–Hillman reaction[14–17] we have examined the possible application of methyl (2*Z*)-2-bromomethylalk-2-enoates‡ **5** derived from methyl 3-hydroxy-2-methylenealkanoates for the synthesis of (*E*)-3-benzylidenechroman-4-ones **8** according to Scheme 1.

We first selected (2*E*)-2-phenoxymethyl-3-phenylprop-2-enoic acid **7a**, which was obtained *via* the reaction of allyl

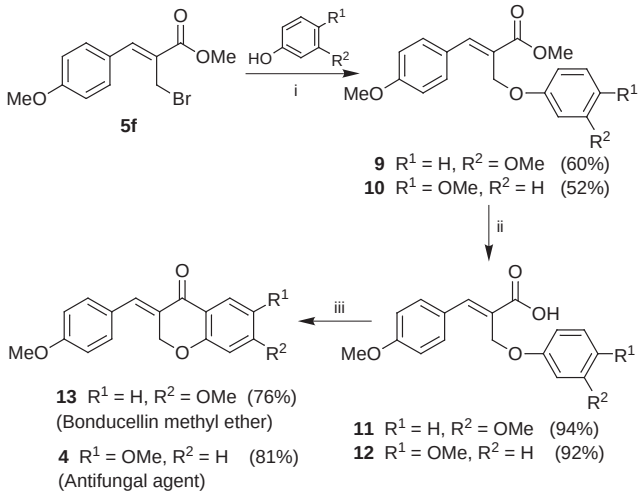


Scheme 1 *Reagents and conditions*: i, PhOH, K_2CO_3, acetone, reflux, 3 h; ii, KOH, H_2O, acetone, room temp., 14 h; iii, TFAA, CH_2Cl_2, reflux, 1 h

Table 1 Synthesis of (*E*)-3-benzylidene- or (*E*)-3-alkylidene-chroman-4-ones (**5**→**6**→**7**→**8**)

Allyl bromide[a]	R	Product[a,b]	Yield[c] (%)	Product[a,d]	Yield[e] (%)	Product[f,g,h]	Yield[i] (%)
5a	Ph	**6a**	73	**7a**	87	**8a**[j]	91
5b	*p*-MeC_6H_4	**6b**	75	**7b**	83	**8b**	94
5c	*o*-MeC_6H_4	**6c**	87	**7c**	93	**8c**	90
5d	*p*-EtC_6H_4	**6d**	90	**7d**	92	**8d**	93
5e	*p*-$Pr^iC_6H_4$	**6e**	71	**7e**	84	**8e**	91
5f	*p*-$MeOC_6H_4$	**6f**	77	**7f**	90	**8f**	92
5g	Pr	**6g**	65	**7g**	78	**8g**	80

[a] See footnote ‖. [b] All reactions were carried out in 10 mmol scale of bromide with 10 mmol of phenol in the presence of K_2CO_3 in acetone at reflux temperature for 3 h. [c] Yields of pure esters obtained after silica gel column chromatography (3% EtOAc–hexane). [d] Hydrolysis of these esters was carried out on a 5 mmol scale with aq. KOH–acetone at room temperature. [e] Isolated yields of the pure acids after crystallization. [f] See footnote **. [g] All the reactions were carried out on a 1 mmol scale for the acid with TFAA (1 mmol) in refluxing CH_2Cl_2 for 1 h. [h] All the products gave satisfactory IR, ^1H NMR (200 MHz), ^{13}C NMR (50 MHz) and mass spectral data and elemental analyses. [i] Yields of the pure chromanones obtained after crystallization (**8a–f**) from EtOAc–hexane (2:98) or after silica gel column chromatography (**8g**) (3% EtOAc–hexane). [j] See footnote §.



Scheme 2 *Reagents and conditions*: i, K_2CO_3, acetone, reflux, 3 h; ii, KOH, H_2O, acetone, room temp., 14 h; iii, TFAA, CH_2Cl_2, reflux, 1 h

bromide **5a**‡ with phenol followed by hydrolysis, as a substrate having a benzylidene moiety. Treatment of **7a** with TFAA in CH_2Cl_2 provided the desired (*E*)-3-benzylidenechroman-4-one **8a**§ in 91% yield. Encouraged by this success we prepared a representative class of (*E*)-3-benzylidenechroman-4-ones **8b**–**f** using (2*E*)-3-aryl-2-phenoxymethylprop-2-enoic acids **7b**–**f** obtained from methyl 3-aryl-3-hydroxy-2-methylenepropanoates (Scheme 1, Table 1). With a view to the generalization of this methodology we also synthesized (*E*)-3-butylidenechroman-4-one **8g** (R = Pr) (Table 1) starting from methyl (2*Z*)-2-bromomethylhex-2-enoate **5g**.¶

The efficiency of this methodology has been demonstrated *via* the synthesis of the methyl ether of bonducellin **13** and (*E*)-3-(4-methoxybenzylidene)-6-methoxychroman-4-one **4**, an antifungal agent, according to Scheme 2.

In conclusion, we have developed a new protocol for the synthesis of (*E*)-3-benzylidenechroman-4-ones involving the initial synthesis of the benzylidene moiety, followed by construction of the chroman-4-one system. Further application of this methodology for the synthesis of biologically active molecules is in progress in our laboratory.

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Footnotes and References

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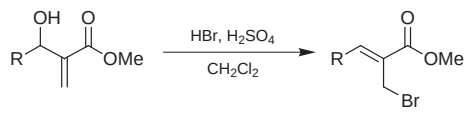
‡ The (*Z*)-allyl bromides **5** were prepared from the corresponding 3-hydroxy-2-methylenealkanoates following the literature method (ref. 18).



§ *Selected data* for **8a**: mp 110–111 °C (lit. 110–112 °C) (ref. 19); ν_{max}(KBr)/cm^{-1} 1668, 1601; δ_H(200 MHz, $CDCl_3$) 5.35 (d, 2 H, *J* 1.6) 6.95–7.60 (m, 8 H), 7.88 (s, 1 H), 8.03 (d, 1 H, *J* 7.8); δ_C(50 MHz, $CDCl_3$) 67.63, 117.93, 121.91, 122.06, 127.96, 128.74, 129.46, 129.99, 130.97, 134.43, 135.85, 137.44, 161.17, 182.17; *m/z* 236 (M^+); Calc. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.45; H, 5.12%.

¶ The reaction of methyl (2*Z*)-2-bromomethylhex-2-enoate **5g** with phenol in the presence of K_2CO_3 also provided *ca.* 15% of a side product, presumably methyl 2-methylene-3-phenoxyhexanoate (S_N2' product). However, the major compound methyl (2*E*)-2-phenoxymethylhex-2-enoate **6g** was obtained in pure form after silica gel column chromatography (3% EtOAc–hexane).

‖ The (*Z*)-stereochemistry of the molecules **5** and the (*E*)-stereochemistry of the molecules **6** and **7** were confirmed by ^{1}H NMR spectral analysis. It is well documented in the literature that in the ^{1}H NMR spectrum the chemical shifts of the vinylic β-proton *cis* to the ketone, ester and acid carbonyl groups and of the corresponding vinylic *trans* β-proton are well-differentiated and vinylic *cis* β-protons appear downfield in comparison with *trans* protons (ref. 20). The (*Z*)-stereochemistry of the allyl bromides **5** was assigned on the basis of the chemical shift values of the β-vinylic protons, *i.e.* δ 7.78–7.91 (when R = Ar) and 6.97 (when R = Pr) (refs. 18, 21). The (*E*)-stereochemistry of the molecules **6, 7** and **9**–**12** was assigned on the basis of the chemical shift values of the β-vinylic protons, *i.e.* δ 8.02–8.25 (when R = Ar) and 6.93–7.11 (when R = Pr) (refs. 18, 22).

** It is well established that in the ^{1}H NMR spectra of 3-benzylidenechroman-4-ones the vinylic β- proton *cis* to the carbonyl group appears at δ *ca.* 7.7 (refs. 4, 23) while the corresponding *trans* β-proton appears at δ *ca.* 6.7 (ref. 4). In the case of compounds **4**, **8a**–**f** and **13** the vinylic β-protons appear at δ 7.81–7.96. Hence (*E*)-stereochemistry was assigned to the compounds **4, 8a**–**f** and **13**. In the case of butylidenechroman-4-one **8g** (R = Pr) the vinylic β-proton appears at δ 7.04. Therefore (*E*)-stereochemistry was assigned to **8g**.

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