Tetrahedron Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Expeditious photochemical reaction toward the preparation of substituted chroman-4-ones

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ARTICLE INFO

Article history:
Received 26 May 2014
Revised 18 June 2014
Accepted 19 June 2014
Available online xxxx

Keywords:
photo-Fries rearrangement
oxa-Michael addition
Aryl esters
Two-phase reaction
Chroman-4-ones

ABSTRACT

A facile photochemical preparation of 5-, 6-, and 7-substituted chroman-4-ones from aryl 3-methyl-2-butenoate esters is described. The two-phase base-catalyzed method relies upon two consecutive processes in one-pot reaction through a photo-Fries rearrangement and a based-catalyzed intramolecular *oxa*-Michael addition to afford the desired products.

The chroman-4-one (2,3-dihydro-4-oxo-4*H*-1-benzopyran) ring system occupies an important position among oxygen heterocycles and features in a wide variety of compounds of biological and medicinal interest.[1] From a synthetic viewpoint, substituted chroman-4-ones are valued both as functional intermediates and as targets in their own right.[2] The chroman parent system has been identified in natural products such as Sappanone B[3] and robustadial[4] in addition to being a bioisostere for the hydantoin moiety. Furthermore, fused-ring chromanones (coumarin and tetrahydroxanthone derivatives) are found in the cores of pseudobruceol I and diversonol.[5] Marine organisms are also a resource of molecules with therapeutic value and puupehenone derivatives belong to this category which is isolated from sponge *Heteronema* sp. and from sponges mainly of the orders *Verongida* and *Dictyoceratida*.[6] (−)-15-Oxopuupehenol is an example of a sesquiterpene and phenolic fusioned moieties that include a benzopyranone scaffold showing antimalarial activity.

Mono- and disubstituted chroman-4-one derivatives are employed in medicine and can be used against a variety of biological processes.[7] Thus, 7,8-dichloro-4-chromanone oximes and novel 3-benzylidene- and 3-benzyl-substituted chromanones can be used to treat or assist in inhibiting a variety of diseases. Therefore, the vast range of biological effects associated with this scaffold has resulted in the chromanone ring system being considered as a privileged structure.[8] Some representative examples are shown in Scheme 1a.

The reported methods for the synthesis of chromanones are well documented and involve (i) condensation of phenols with 3,3-dimethyl acrylic acids or its derivatives (Friedel–Craft reaction together with thermal Fries rearrangement); (ii) Claisen rearrangement of propargyl ethers of phenols and, (iii) Knoevenagel condensation of *o*-hydroxyphenones with aliphatic aldehydes and ketones (Kabbe reaction).[9] The last method perhaps is the most convenient and practical procedure involving the base-catalyzed condensation between a 2-hydroxyphenone and an aldehyde.

However, an alternative methodology scarcely considered is the photo-Fries rearrangement reaction as a key step in the preparation of chroman-4-ones (see Scheme 1b).[10] Recently, we have reported a mild and convenient one-pot photochemical synthesis of several chroman-4-one derivatives under a biphasic base catalysis system in good to high yield.[11] Since we are interested in the application of the photo-Fries rearrangement reaction in organic synthesis, in order to ascertain scope and limitations of the methodology, we report the photochemical reaction of a series of *p*- and *m*-substituted esters **2a**–**o** under a one-pot base-mediated photochemical reaction to afford a variety of substituted chroman-4-one derivatives with good yield and noticeable regioselectivity. The general synthetic approach and experimental conditions are shown in Scheme 2.

The commercially available substituted phenols **1a**–**o** were allowed to react with 3-methyl-2-butenoate chloride in dry pyridine at room temperature within 60 min. The molar ratio of the acylating reagent to phenols was 1.1 to 1.2. After acidic work-up and chromatographic purification esters **2a**–**o** were obtained in

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http://dx.doi.org/10.1016/j.tetlet.2014.06.081
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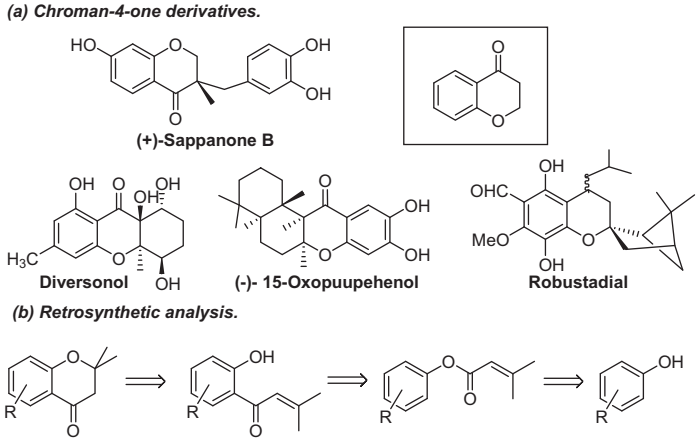
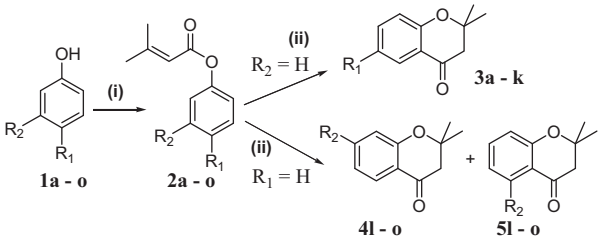


Scheme 1. Natural compounds containing benzopyranone scaffold and proposed retro-synthesis.



R_2 = H R_1 = H (**1a**); CH_3 (**1b**); Cl (**1c**); NO_2 (**1d**); OMe (**1e**); OPh (**1f**); Ph (**1g**); *t*-Bu (**1h**); $CO(CH_2)_3CH_3$ (**1i**); CN (**1j**); $COOCH_3$ (**1k**).
R_1 = H R_2 = CH_3O (**1l**); CH_3 (**1m**); Cl (**1n**); NO_2 (**1o**).

Scheme 2. Reagents and conditions: (i) 3-methyl-2-butenoyl chloride (1.1 equiv), pyridine, 25 °C, 10–60 min; (ii) hν (254 nm), cyclohexane–KOH 10% aq (8:2), 60–120 min, 25 °C, Ar.

excellent yields (>90%) and were fully characterized by means of physical and spectroscopic methods (see Supplementary material). The above acylation reactions of compounds **1a**–**o** were also performed in anhydrous benzene or dichloromethane in the presence of dry pyridine. However, the yields dropped dramatically and the reactions required longer time; moreover, reaction completion was not achieved, recovering the starting material in significant extent.

Next, we embarked on a systematic examination of the photochemical reaction of eight 4-substituted esters **2b**–**k** bearing electron-withdrawing and electron-donating groups in order to explore the scope of the one-pot photochemical synthesis of chroman-4-one derivatives. Thus, the irradiation of esters **2b**–**k** was carried out with an excitation wavelength of 254 nm, in a biphasic system (cyclohexane–KOH 10% aq) as the reaction medium, under inert atmosphere (Ar) and room temperature. This optimized condition was recently applied for the photochemical reaction of ester **2a** that gratifyingly gave 2,2-dimethyl-chroman-4-one (**3a**) in quantitative yield (see Table 1, entry 1).[11] Therefore, we decided to apply this optimized methodology to esters **2b**–**k**.

As shown in Table 1, a variety of 4-substituted esters **2** were employed as reaction substrates and the photochemical reaction can afford the corresponding chroman-4-one derivatives in good to excellent yields regardless of the different substitutions on the aromatic ring. Clearly, substrate with an electron-donating group on the aromatic ring gave a better yield than that of an electron-withdrawing group on the aromatic ring when the organic solvent of the biphasic system is cyclohexane. For example, substrates with alkyl, aryl, methoxy, or phenoxy group, the yields of the corresponding chroman-4-ones were obtained in good to quantitative

Table 1
photo-Fries rearrangement reaction of p-substituted phenyl 3-methyl-2-butenoate esters (**2a–i**) in cyclohexane under basic catalysis (KOH 10% aq; biphasic system)[a]

Entry	Substrate; R	Irradiation time (min)	Conv. %	Yield[b] %
1	**2a**; H[c]	60	70	**3a**; 100
2	**2b**; CH_3	90	95	**3b**; 86
3	**2b**; CH_3[d]	120	100	**3b**; 95
4	**2c**; Cl	90	95	**3c**; 71
5	**2c**; Cl[d]	115	94	**3c**; 95
6	**2d**; NO_2	105	79	**3d**; 40[e]
7	**2d**; NO_2[f]	105	80	**3d**; 98[g]
8	**2e**; MeO	60	100	**3e**; 100
9	**2f**; PhO	60	98	**3f**; 100
10	**2g**; Ph	90	95	**3g**; 96
11	**2h**; *t*-Bu	125	100	**3h**; 90
12	**2i**; $CO(CH_2)_3CH_3$	100	92	**3i**; 94
13	**2j**; CN	90	95	**3j**; 96
14	**2k**; $COOCH_3$	120	95	**3k**; 90

[a] Reaction conditions: 0.010 M of ester, excitation wavelength: 254 nm, quartz vessel, degassed solvent (2.5 mL), under Ar, room temperature.
[b] The yields are based on the conversion of the starting material.
[c] Data taken from Ref. 11.
[d] Standard conditions, organic solvent/benzene.
[e] The *p*-nitrophenol was formed in 53% yield.
[f] Standard conditions, organic solvent/benzene; base catalyst/Cs_2CO_3 (s).
[g] The *p*-nitrophenol was formed in 2% yield.

yields (Table 1, entries 2, 8–11). Besides, substrates with electron-withdrawing groups (chloro, methylketone, cyano or methyl carboxylate groups) in the phenyl ring afforded the corresponding chroma-4-one in good yields (Table 1, entries 4, 12–14). Irradiation of compound **2d** under our optimized conditions afforded the corresponding chroman-4-one **3d** in low yield together with significant amount of 4-nitrophenol (Table 1, entry 6). This behavior is due to a competitive photo solvolysis process of ester **2d**. When benzene is used instead of cyclohexane, the irradiation of esters **2b**, **2c**, and **2d** afforded the corresponding chroman-4-one derivatives **3b**, **3c**, and **3d** in good yields, respectively (Table 1, entries 3, 5 and 7). It is interesting to point out that for ester **2d** the photochemical reaction was accomplished in benzene and in the presence of Cs_2CO_3 as the base catalyst to improve the yield of **3d** and to diminish the formation of the 4-nitrophenol.

Since our method showed that it is easy to obtain 6-substituted chroman-4-one derivatives, we decided to extend this efficient and optimized photochemical reaction to a series of *m*-substituted esters **2l**–**o** in order to prepare the corresponding 5- and 7-substituted chroman-4-one derivatives. As is shown in Table 2, the expected regioisomers **4** and **5** were obtained in good yields

in a ca. 1:1 M ratio regardless of the electron-donating or electron – withdrawing nature of the substituent attached to the aromatic ring of esters **2** with the exception of the nitro group (**2o**). These results can be rationalized taking into account the charge density values of C-2 and C-6 that belong to the aromatic ring of esters **2l–o**. Therefore, we have calculated the charge densities of all the carbon atoms by AM1 Semi Empirical calculation of esters **2** (see Supplementary material). Since both atom positions, viz. C-2 and C-6, show similar values, it is expected that migration of the acyl group would proceed to both positions with similar probability during the photochemical process, which is the photo Fries step that provides the *o*-hydroxy phenone intermediates. Then, in a second step, the intramolecular *oxa*-Michael addition reaction takes place efficiently under base-mediated catalysis onto both *o*-hydroxy phenone intermediates (see Scheme 3 and Table 3). However, the charge density values at C-6 are slightly greater than those values at C-2 and a nice correlation is observed between these values and the respective yields of formation of chroman-4-ones **4** and **5**, respectively. It is also interesting to point out that since charge density values at C-4 predict that the *p*-hydroxyphenone derivatives could be formed with similar probability as compounds **4** and **5**, in our experimental conditions this kind of photoproduct was not detected, however.

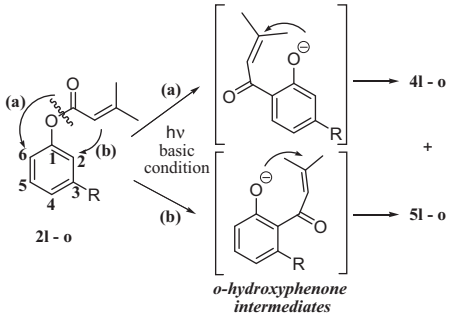
Again, the nitro compound **2o** shows a different behavior. The chroman-4-one **4o** was obtained in moderate yield with a high regioselectivity, along with significant amount of *m*-nitrophenol. The use of Cs_2CO_3 as catalyst was beneficial to accomplish the photochemical reaction, whereas, the use of KOH favored the formation of *m*-nitrophenol in high yield, giving compound **4o** in low yield (see Table 2, entries 5 and 6). The regioselectivity observed for ester **2o** can be rationalized in terms of the charge density values. Since in ester **2o** C-6 shows a higher charge density than C-2, it is expected that the acyl group will migrate preferentially to C-6 than to C-2. Therefore, chroman-4-ones **4o** and **5o** will be obtained with noticeable selectivity. Compound **4o** was indeed obtained in moderate yield as it was predicted by the Semi Empirical AM1 method, while compound **5o** was not formed.

The success of the thermal cyclization reaction of esters **2a–o** can be ascribed to the polarization of the double bond, due to conjugation with the ketone group that determines the occurrence of the nucleophilic attack exclusively at C-β of the double bond, in agreement with the usual reactivity of α,β-ethylenic carbonyl compounds.[12] Furthermore, the success of the intramolecular *oxa*-Michael addition is improved in our experimental conditions due to the formation of the phenoxide ion of the *o*-hydroxyphenone intermediate under basic catalysis. In this regard, the phenoxide ion becomes a better nucleophile than the hydroxy group promoting the nucleophilic attack at C-β of the double bond efficiently to afford chroman-4-one derivatives in high yields.

Table 2
photo-Fries rearrangement reaction of m-substituted phenyl 3-methyl-2-butenoate esters (**2l–o**) in cyclohexane under basic catalysis (KOH 10% aq; biphasic system)[a]

Entry	Substrate; R	Irradiation time (min)	Conv. %	Yield[b] %
1	**2l**; OCH_3	65	95	**4m**, 51; **5m**, 42
2	**2m**; CH_3	65	90	**4n**, 50; **5n**, 39
3	**2n**; Cl	105	65	**4o**, 51; **5o**, 41
4	**2o**; NO_2[c]	40	34	**4p**, 59[e]; **5p**, 0
5	**2o**; NO_2[d]	70	10	**4p**, 30[f]; **5p**, 0

[a] Reaction conditions: 0.010 M of ester, excitation wavelength: 254 nm, quartz vessel, degassed solvent (2.5 mL), under Ar, room temperature.
[b] Yields are based on the conversion of the starting material.
[c] Standard conditions, base catalyst/Cs_2CO_3 (s).
[d] Standard conditions, solvent/benzene–KOH 10% aq.
[e] *m*-nitrophenol was formed in 17.6% yield.
[f] *m*-nitrophenol was formed in 70% yield.



Scheme 3. Formation of chroman-4-ones **4** and **5** under two-phase base-mediated photochemical reaction.

Table 3
Charge density values of esters **2l–o** calculated with the Semi Empirical AM1 method[a]

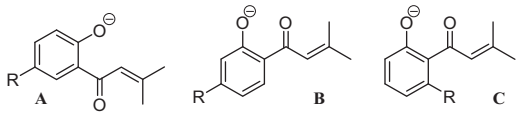
Compd; R	Charge density values					
	C-1	**C-2**	**C-3**	**C-4**	**C-5**	**C-6**
2l; OCH_3	0.085	−0.212	0.093	−0.165	−0.086	−0.189
2m; CH_3	0.055	−0.136	−0.054	−0.141	−0.112	−0.162
2n; Cl	0.063	−0.131	−0.048	−0.135	−0.107	−0.158
2o; NO_2	0.051	−0.077	−0.116	−0.081	−0.124	−0.120

[a] Carbon atom numbering see Scheme 3.

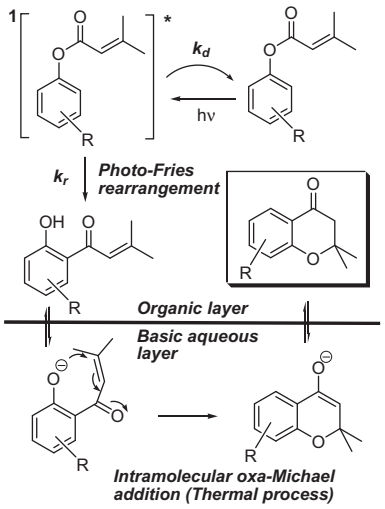
We have also calculated the charge densities by the Semi Empirical AM1 method for all the phenoxide ions of the *o*-hydroxyphenone intermediates formed after the photo-Fries rearrangement has occurred. The relevant data of interest are the charge densities belonging to the oxygen of the fenoxide ion and the C-β of the α,β-ethylenic moiety which are collected in Table 4. The calculated data predict that the cyclization process could take place efficiently and, in fact, this prediction is in agreement with our experimental results.

With regard to mechanism, the findings herein and from previous studies[10c,11] led us to surmise that these biphasic photoreactions advance via 2-hydroxyphenone intermediates which is formed during the photolysis of esters **2a–o** and do not need to be isolated. To rationalize the reaction mechanism we proposed that the whole photochemical reaction of esters **2a–o** takes place actually in two consecutive steps: (i) the photochemical formation of the rearrangement product (*o*-hydroxy phenone) and (ii) the thermal intramolecular cyclization of the *o*-regioisomer to the

Table 4
Charge density values of phenoxide ion of the *o*-hydroxyphenone intermediates **A**, **B**, and **C**, calculated with the Semi Empirical AM1 method



R	Charge densities					
	A		B		C	
	Ar–O⁻	C-β	Ar–O⁻	C-β	Ar–O⁻	C-β
OCH_3	−0.496	−0.103	−0.494	−0.103	−0.492	−0.105
OPh	−0.478	−0.095	—	—	—	—
t-Bu	−0.493	−0.103	—	—	—	—
CH_3	−0.495	−0.104	−0.490	−0.105	−0.499	−0.107
H	−0.498	−0.105	−0.498	−0.105	−0.498	−0.105
Cl	−0.485	−0.097	−0.484	−0.097	−0.487	−0.102
NO_2	−0.445	−0.078	−0.468	−0.005	−0.477	−0.085



Scheme 4. Proposed reaction mechanism.

corresponding chroman-4-one through an intramolecular *oxa*-Micheal addition reaction. A simplified mechanism for this reaction is shown in Scheme 4, where k_d means all the deactivation processes (fluorescence emission and internal conversion) that compete with the photochemical reaction k_r.

Finally, we have measured the quantum yield (ϕ_r) of the biphasic photochemical reaction of esters **2a**–**o** using potassium ferrioxalate as an actinometer.[13] The ϕ_r values range between 0.30 and 0.50 indicating that the photoreaction is efficient and competes with the deactivation processes of the singlet excited state, namely, fluorescence emission and internal conversion.

In summary, we showed the scope and applicability of the one-pot photochemical biphasic system for the preparation of 5-, 6-, and 7-substituted chroman-4-one derivatives starting from *p*- and *m*-substituted aryl 3-methyl-2-butenoate esters. The esters are easily prepared from commercially available substituted phenols. With the application of this photochemical method, a series of substituted chroman-4-one derivatives were prepared from moderate to quantitative yields. Finally, this method exhibits predictable regioselectivity and can be considered as a general and wide useful and inexpensive methodology.

Acknowledgments

The authors thank Universidad de Buenos Aires (X088 and X372), CONICET (PIP0040 and PIP0155) for financial support. R. Erra-Balsells and S. M. Bonesi are research members of CONICET. D. Iguchi thanks CONICET for doctoral scholarship (Doctorate Program).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.06.081.

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