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A mild and convenient one-pot photochemical synthesis of chroman-4-one derivatives. The photo-Fries rearrangement of (hetero)aryl 3-methyl-2-butenoate esters under basic catalysis

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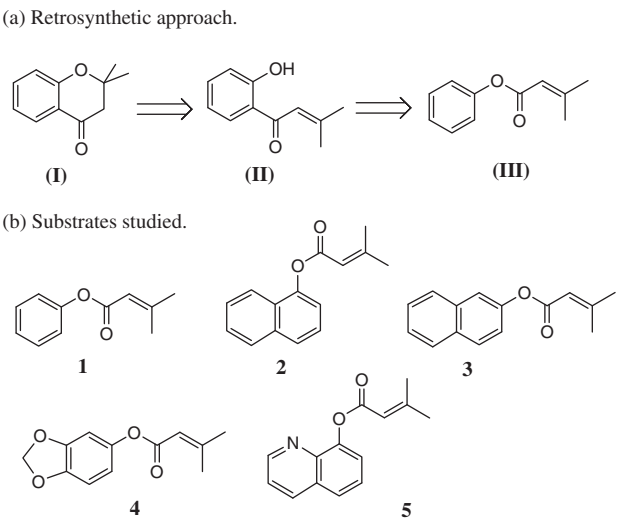
ABSTRACT

The biphasic base catalysis-mediated photo-Fries rearrangement reaction of aryl 3-methy-2-butenoate esters in room temperature cyclohexane—10% KOH system was investigated. This mild photochemical reaction leads to the formation of chroman-4-one derivatives in good to high yield and in short reaction times (30–120 min) in a one-pot photochemical reaction. Also, the photochemical reaction, as a convenient, versatile, and general method, applies efficiently to polycyclic and heterocyclic 3-methy-2-butenaoate esters.

The synthesis, chemistry, occurrence in nature, and biological activity of chromanones have been the subject of several comprehensive reviews.[1] Chroman-4-ones are also important synthetic intermediates for chromans, chromenes, and chromanols which themselves posses diverse pharmacological properties such as β-blockade, anticonvulsant, antiestrogen, and antimicrobial.[1c] Precocenes are modern pesticides with potent insect antijuvenile hormone agents[2] and cromakalim and related analogues, which are discovered potassium channel openers,[3] contain the benzopyrane moiety. Also, mollugin, dihydrolapachenole, lapachenole, and their 6-methoxyderivatives contain the 2,2-dimethylnaphtho[1,2-*b*]pyran moiety in their structures and show biological activity.[4,5]

Because of their widespread occurrence and valuable properties, numerous syntheses have been developed for the construction of chroman-4-ones.[6] The reported methods for the synthesis of chroman-4-ones and benzochroman-4-ones are well documented and involve: (i) condensation of phenols with 3,3-dimethylacrylic acids or its derivatives (Friedel–Craft reaction together with thermal Fries rearrangement);[7] (ii) Claisen rearrangement of propargyl ethers of phenols;[8] and (iii) Knoevenagel condensation of *o*-hydroxyacetophenones with aliphatic aldehydes and ketones (Kabbe reaction).[9] Perhaps the most convenient and practical method is the base-catalyzed Knoevenagel condensation between a 2-hydroxyacetophenone and an aldehyde. In turn, the requisite acetophenones are usually readily available via a thermal Fries rearrangement of the adduct obtained from an appropriate acid (or derivative thereof) and a substituted phenol.[10]

An alternative methodology scarcely considered is the photo-Fries rearrangement reaction as a key step in the synthesis of chroman-4-ones depicted in Scheme 1a. Thus, *o*-hydroxy ketone derivative **II** is an adequate key intermediate that can be easily achieved after a photo-Fries rearrangement reaction of phenyl 3-methyl-2-butenoate ester **III**. Cyclization reaction of synthon **II** could be carried out using different methodologies such as a base (K_2CO_3, NaOH, PhONa, Et_3N, piperidine, and morpholine) in reflux-



Scheme 1. Aryl 3-methyl-2-butenoate esters studied and retrosynthetic analysis of 2,2-dimethyl-chroman-4-one.

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ing ethanol[11] or K_2CO_3 in acetone[12] at room temperature, where the target molecule **I** is obtained in good chemical yield. Our proposed alternative synthetic approach can be accomplished in a one-pot base-mediated irradiation of compound **III** to afford directly the target molecule **I** without isolation of synthon **II**. According to our knowledge, Miranda et al. have only synthesized the 6-methoxy-2,2-dimethylchroman-4-one and 6-methoxy-2-methylchroman-4-one using the biphasic base-mediated photochemical reaction successfully.[13] Since the discovery of the photo-Fries rearrangement reaction in 1960[14], mechanistic elucidation of the reaction rather than its use in synthesis has been devoted.[15–18] Since the photo-Fries rearrangement of aryl 3-methyl-2-butenoate esters **1**–**5** (see Scheme 1b) has not been investigated under base catalysis conditions[19] and, due to our interest on the photo-Fries reaction,[20] herein we report the photochemical studies of esters **1**–**5** in a biphasic base catalysis system to afford directly chroman-4-ones in good to high yield.

To begin we simply subjected ester **1** to our photochemical conditions. Gratifyingly, these conditions afforded quantitatively 2,2-dimethyl-chroman-4-one (**1a**) within 60 min (Table 1, entry 3). To build from this result, the photoreaction of ester **1** was screened against different base sources, acid sources, solvents, and different excitation wavelength.

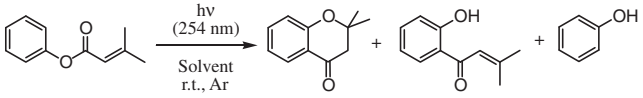
In the absence of base no chroman-4-one **1a** formation was seen after 120 min of irradiation. Instead, the expected photo-Fries products were formed in fairly good yield (see Table 1, entry 1). Then, changing the base source a noticeable drop of the yield of **1a** was observed together with significant amounts of compounds **1b** and **1c** (see Table 1, entries 2 and 4). Thus, the use of the biphasic system cyclohexane—KOH 10% aq is the optimized condition for the photochemical reaction of ester **1** giving 2,2-dimethyl-chroman-4-one (**1a**) in quantitative yield (see Table 1, entry 3).

The use of benzene instead of cyclohexane in the biphasic system for the photochemical reaction of **1** affords quantitatively compound **1a**. Besides, irradiation of **1** in acetonitrile in the presence of triethylamine (homogeneous system) gives phenol (**1c**) in 95% yield due to a photo solvolysis process induced by the amine (see Table 1, entries 5 and 6, respectively). We also carried out the photochemical reaction of **1** in the presence of perchloric acid (homogeneous system) and again compound **1c** was formed in quantitative yield through a photo solvolysis process. Besides, irradiation of **1** with our standard condition but under oxygen atmosphere affords compound **1c** in 89% yield and some brownish tarry residue is also formed (Table 1, entry 8). Therefore, the photochemical reactions were carried out under Argon atmosphere (bubbling the biphasic system during 20 min before irradiation).

In order to analyze the effect of the excitation wavelength on the biphasic base catalysis—mediated photochemical reaction additional experiments were carried out. Thus, the photochemical reaction of **2** under basic catalysis was performed at two different wavelengths, 254 and 313 nm, and 2,2-dimethylnaphtho[1,2-*b*]pyran-4-one (**2a**) was obtained in 93% and 95% yield, respectively (compare entries 1 and 2 in Table 2). Similar results were obtained when ester **3** was irradiated at two different excitation wavelengths (compare entries 4 and 5 in Table 2) and chroman-4-one (**3a**) was formed in high yield. Also, irradiation of ester **2** using benzene instead of cyclohexane, as the organic solvent of the reaction system, affords chroman-4-one **2a** in nearly quantitative yield (see entry 3 in Table 2). These results mean that the lowest singlet excited state, which is most likely to be π,π^* excited state,[21] is the photo reactive excited state of esters **2** and **3**. Photosensitization experiment of **2** with benzophenone (λ_{exc}: 366 nm), which is a triplet—energy donor,[21] does not afford the chroman-4-one **2a**. In this regard, the lowest triplet excited state of ester **2**, if it is populated efficiently, does not give any photoproducts and deactivates through a radiationless process.[20b–d,21] Thus, our optimal conditions were determined to be the first condition examined, namely, 0.010 M of esters, *hν* (254 or 313 nm) in a biphasic system (cyclohexane (2.5 mL) and KOH 10% aq (0.5 mL)) under Argon atmosphere at room temperature. To the best of our knowledge, this is the first example of a one-pot photochemical reaction of esters of the type **1**–**5** for the synthesis of 2,2-dimethyl chroman-4-one derivatives. Also, the procedure is much simpler, milder, regioselective than other thermal reactions that need the use of Lewis acids and harsh conditions (i.e. high reaction temperature).[7,8,5]

Extension of the methodology to heteroaryl esters **4** and **5** afforded the chroman-4-one derivatives in high yields. It is interesting

Table 1
Photo-Fries rearrangement reaction of phenyl 3-methyl-2-butenoate ester (**1**)[a]

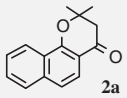
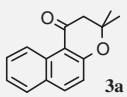
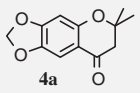
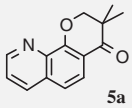


1 **1a** **1b** **1c**

Entry	Conditions [Irradiation time (min)]	Conv. (%)	Yield (%)		
			1a	**1b**	**1c**
1	Cyclohexane [120]	90	—	41[b]	21
2	Cyclohexane K_2CO_3 10% aq [60]	69	22	47	—
3	Cyclohexane KOH 10% aq [60]	70	100	—	—
4	Cyclohexane Et_3N 0.10 M [60]	93	26	25	30
5	Benzene KOH 10% aq [100]	95	100	—	—
6	MeCN Et_3N 0.10 M [75]	100	—	5	95
7	MeCN $HClO_4$ 0.10 M [75]	100	—	—	100
8	Cyclohexane KOH 10% aq[c] [60]	70	89	—	—

[a] Reaction conditions: 0.010 M of **1**, excitation wavelength: 254 nm, quartz vessel, degassed solvent (2.5 mL), under Ar, room temperature. The yields are based on the conversion of the starting material.
[b] The *para*-isomer (**1d**) was also formed in 22% yield.
[c] Standard condition, *non*-Argon degassed solution.

Table 2
Photo-Fries rearrangement reaction of (hetero)aryl 3-methyl-2-butenoate esters (**2**–**5**) in cyclohexane under basic catalysis (KOH 10% aq; biphasic system)[a]

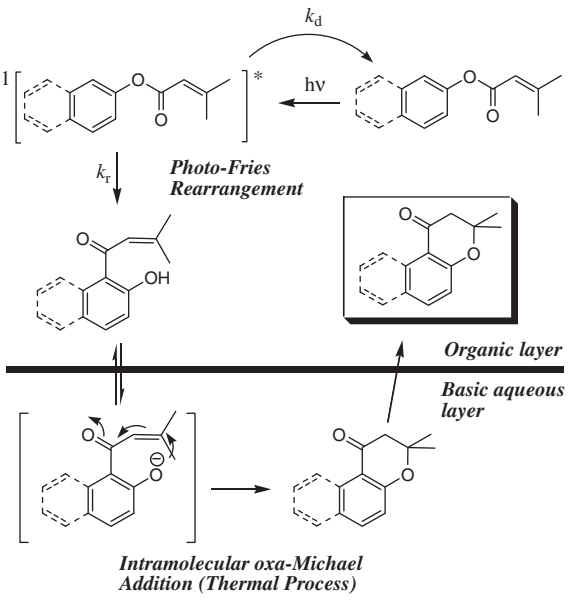
Entry	Esters	Δ*t* (min)	Conv. (%)	Yield (%)	
1	**2**	10	100	95[d]	 **2a**
2		10[b]	100	93[d]	
3		10[c]	100	95[d]	
4	**3**	30	100	89	 **3a**
5		30[b]	100	95	
6	**4**	30	90	100	 **4a**
7	**5**	40	100	100	 **5a**

[a] Reaction conditions: 0.010 M of ester, excitation wavelength: 310 nm, quartz vessel, degassed solvent (2.5 mL), under Ar, room temperature. The yields are based on the conversion of the starting material.
[b] Standard conditions, excitation wavelength: 254 nm.
[c] Standard conditions, organic solvent: benzene, excitation wavelength: 310 nm.
[d] 2-(1-Hydroxynaphthyl) isobutenyl ketone (**2b**) was formed in 5–6% yield.

to note that the 3,4-(methylenedioxy)phenyl 3-methyl-2-butenoate (**4**) gave only one chroman-4-one derivative, the compound **4a**, in our standard condition in quantitative yield (30 min of irradiation) with a noticeable regioselectivity (see entry 6 in Table 2). The stereo-electronic repulsion between the n electrons of the carbonyl oxygen and the oxygen of the 3,4-methylenedioxy moiety accounts for the regioselectivity observed. Likewise, 8-quinolyl 3-methyl-2-butenoate (**5**) is easily photocyclized to the corresponding chroman-4-one derivative **5a** in quantitative yields and in 40 min according to our standard conditions (see Table 2, entry 7). The results shown in Table 2 prove that the biphasic base catalysis-mediated photo-Fries rearrangement reaction of esters **2**–**5** is a mild and general method for the synthesis of chroman-4-one derivatives in high yields and with a noticeable regiochemistry.

With regard to mechanism, the findings herein and from other studies[13] led us to surmise that these biphasic photoreactions advance via 2-hydroxyphenone intermediates which are formed during the photolysis of esters **1**–**5** and do not need to be isolated. To rationalize the reaction mechanism we proposed that the whole photochemical reaction of esters **1**–**5** takes place really in two consecutive steps: (i) the formation of the rearrangement product (*ortho*-hydroxy ketone) photochemically and (ii) the thermal intramolecular cyclization of the *ortho*-isomer to the corresponding chroman-4-one through an intramolecular *oxa*-Micheal addition reaction. A simplified mechanism for this reaction is shown in Scheme 2, where k_d means all the deactivation processes (fluorescence emission and internal conversion) that compete with the photochemical reaction k_r. The success of the thermal reaction 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(3) of the double bond, in agreement with the usual reactivity of α,β-ethylenic carbonyl compounds.[11d,e] 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 2-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(3) of the double bond efficiently to afford chroman-4-one derivatives in high yields.

Besides, we have measured the quantum yield (φ_r) of the biphasic photochemical reaction of esters **1**–**5** using potassium ferrioxalate as an actinometer.[22] The φ_r values range between 0.25 and 0.40 indicating that the photoreaction is efficient and competes with the deactivation processes of the photo reactive singlet excited state, namely, fluorescence emission and internal conversion.



Scheme 2. Proposed reaction mechanism.

In summary, biphasic base catalysis-mediated photo-Fries rearrangement reactions of esters **1**–**5**, rapidly and mildly afford chroman-4-one, benzochroman-4-one, and heteroarylchroman-4-one derivatives in good to high yields at room temperature. The whole reaction is initiated through a photo-Fries rearrangement at different excitation wavelength followed by a base catalysis cyclization, namely, an intramolecular *oxa*-Michael addition reaction, of the 2′-hydroxyphenone intermediate. Also, this synthon does not need to be isolated from the photolyzed system. This method exhibits predictable regioselectivity, applies efficiently to polycyclic and heterocyclic aryl 3-methyl-2-butanoate esters, takes place in a one-pot fashion reaction, and can be considered as a general and wide useful methodology. Finally, the method is inexpensive, with simple work-up and does not need the use of Lewis acid agents and harsh thermal conditions.

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Supplementary data

Supplementary data (general method and spectroscopic characterization of starting materials and photoproducts) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.063.

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