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Tandem synthesis of 4-aminoxanthones is controlled by a water-assisted tautomerization: a general straightforward reaction†

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Aminoxanthones constitute a group of therapeutically promising compounds that so far have been synthetically challenging. Here, we report the synthesis of both aminodihydroxanthones and fully aromatized aminoxanthones by an easy to perform, one-step multicomponent reaction of isocyanides, 3-carbonylchromones and dienophiles. The mechanism of the reaction involves a sequence of a [4 + 1] cycloaddition, iminolactone-aminofuran tautomerization, [4 + 2] cycloaddition, oxygen ring opening and aromatization. Remarkably, DFT quantum chemical computations revealed that the iminolactone-aminofuran tautomerization requires the assistance of a water molecule and, contrary to intuition, it is the rate-determining step. Conversely, both the [4 + 1] and the [4 + 2] cycloadditions have relatively low calculated energy barriers, regardless the substituents on the starting materials. Thus, we have stablished a straightforward and a wide-ranging synthesis of diversely substituted xanthones. This highly convergent process has also been applied to the synthesis of biologically important chromenophenantridines and secalonic acid related xanthone dimers.

Introduction

Xanthones are secondary metabolites occurring in many plants, fungi, lichens and bacteria.[1] They exist as either partially hydrogenated or fully aromatized derivatives and often exhibit distinct biological activities, which depend on the degree of oxidation of the rings and their substitution pattern.[2] Many biologically active xanthones contain hydrogen bond donating or accepting substituents, such as hydroxyl or amino groups, which facilitate key interactions with their biological targets.[3] For instance, aminoxanthones have been proposed as chemotherapeutic agents for the treatment of diseases, such as diabetes, HIV, and multidrug resistant cancers, due to their interaction with negatively charged nucleic acids, proteins and cell substructures.[4]

Although different methods for the synthesis of xanthones are available, they are mostly limited to fully aromatized derivatives. Moreover, the introduction of amino substituents almost invariably implies long, indirect procedures and harsh reaction conditions.[5] Additionally, literature reports on the synthesis of biologically relevant dimeric xanthones are relatively scarce, making them synthetically challenging targets.[6] In a recent work, we have reported the generation of 2-aminofuranes by a [4 + 1] cycloaddition of α,β-unsaturated carbonyl compounds and isocyanides. These 2-aminofuran intermediates have been conveniently trapped *in situ* with dienophiles to give anilines with good yields.[7] We have found that 4-aminodihydroxanthones (**7**)[8] and 4-aminoxanthones (**8**)[9] could be prepared through a similar tandem [4 + 1]–[4 + 2] cycloaddition of 3-carbonylchromones (**1**), isocyanides (**2**) and dienophiles (**3**) (Scheme 1).

The mechanism of the reaction is explained by a [4 + 1] cycloaddition of the 3-carbonylchromone (**1**) with the isocyanide (**2**) to give an iminolactone intermediate (**4**). Tautomerization to aminofuran (**5**), which suffers a [4 + 2] cycloaddition with the dienophile (**3**), leads to 7-oxabicyclo [2.2.1]heptane (**6**). This is readily transformed to 1-hydroxydihydroxanthone (**7**) by the opening of the oxygen bridge assisted by the nitrogen lone pair. Dehydration finally affords the aromatic 4-aminoxanthone (**8**; Scheme 1).

So far, this reaction was limited to electron-poor chromones such as those containing electron-withdrawing groups attached to the carbonyl, which we thought would favour the first [4 + 1] cycloaddition leading to the purportedly highly reactive 2-aminofuran intermediate.[8,9]

In this full paper, we demonstrate that it is possible to extend this methodology[8,9] to synthesize diversely substituted

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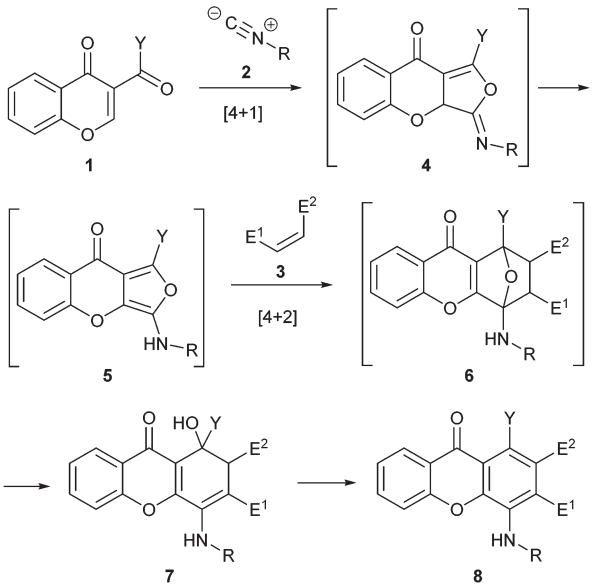


Scheme 1 Our synthesis of xanthones and dihydroxanthones.

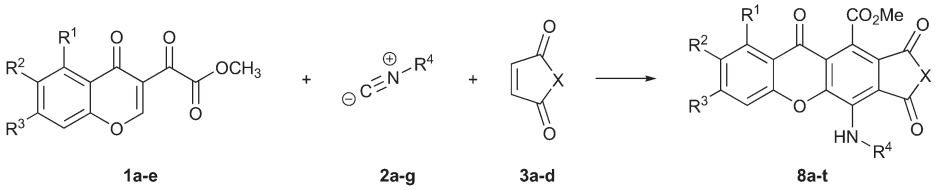
xanthones and dihydroxanthones, starting from carbonylchromones containing both electron-withdrawing and electron-donating groups. A complete theoretical mechanistic study has been performed in order to delimitate the scope and limitations of this process.

Results and discussion

Electron-poor 3-methoxalylchromone (**1a**, Table 1), in which a CO_2CH_3 substituent is on the carbonyl group, was initially chosen as starting material in order to facilitate the formation of the 2-aminofuran, which we hypothesized would rapidly react with the dienophile.[9] To our delight, the reaction of methoxalylchromones (**1a–e**), isocyanides (**2a–g**) and cyclic maleic acid derivatives (**3a–d**) in THF at 25–35 °C readily afforded 4-aminoxanthone-1-carboxylates (**8a–t**) with yields up to 99% (Table 1). Reaction times range from 24 to 144 h and the products were isolated with high purity by simple filtration from the reaction medium.

The process shows wide tolerance to different substituents on the chromone core, isocyanides and maleic acid derivatives. As a result, xanthones with diverse substituents on both aromatic rings are obtained. However, a closer analysis of the results displayed in Table 1 show that, unexpectedly, donor substituents on the chromone aromatic ring, such as 7-methoxy (Table 1, entry 8) and 6-methyl (Table 1, entry 10) seem to facilitate the overall process, considerably reducing the time of the reaction. Conversely, the electron-withdrawing group-containing 6-chlorochromone requires longer reaction times and/or higher temperatures (Table 1, entries 9, 12 and 20). These results are not consistent with the initial mechanistic hypothesis of a slow [4 + 1] cycloaddition followed by a rapid

Table 1 General synthesis of 4-aminoxanthones from methoxalylchromones (**1a–e**)[a]



1a-e **2a-g** **3a-d** **8a-t**

Entry	Chromone	R^1	R^2	R^3	Isocyanide	R^4	Dienophile	X	*T*, °C	Time, h	Product (yield, %)
1	**1a**	H	H	H	**2a**	*c*-C_6H_{11}	**3a**	*N*-C_6H_5	35	96	**8a** (99)
2	**1a**	H	H	H	**2b**	*t*-Bu	**3a**	*N*-C_6H_5	35	96	**8b** (93)
3	**1a**	H	H	H	**2c**	2,6-$Me_2C_6H_3$	**3a**	*N*-C_6H_5	35	144	**8c** (67)
4	**1a**	H	H	H	**2d**	$PhCH_2$	**3a**	*N*-C_6H_5	35	78	**8d** (93)
5	**1a**	H	H	H	**2e**	C_5H_{11}	**3a**	*N*-C_6H_5	35	22	**8e** (97)
6	**1a**	H	H	H	**2f**	4-$MeOC_6H_4$	**3a**	*N*-C_6H_5	35	22	**8f** (99)
7	**1a**	H	H	H	**2g**	CH_2CO_2t-Bu	**3a**	*N*-C_6H_5	35	49	**8g** (82)
8	**1b**	H	H	OMe	**2a**	*c*-C_6H_{11}	**3a**	*N*-C_6H_5	25	24	**8h** (99)
9	**1c**	H	Cl	H	**2a**	*c*-C_6H_{11}	**3a**	*N*-C_6H_5	35	96	**8i** (81)
10	**1d**	H	Me	H	**2a**	*c*-C_6H_{11}	**3a**	*N*-C_6H_5	25	24	**8j** (75)
11	**1e**	Benzo		H	**2a**	*c*-C_6H_{11}	**3a**	N-C_6H_5	25	140	**8k** (30)
12	**1c**	H	Cl	H	**2b**	*t*-Bu	**3a**	*N*-C_6H_5	35	120	**8l** (85)
13	**1a**	H	H	H	**2a**	*c*-C_6H_{11}	**3b**	*N*-CH_3	35	32	**8m** (94)
14	**1b**	H	H	OMe	**2a**	*c*-C_6H_{11}	**3b**	*N*-CH_3	35	23	**8n** (81)
15	**1a**	H	H	H	**2a**	*c*-C_6H_{11}	**3c**	O	25	96	**8o** (83)
16	**1b**	H	H	OMe	**2a**	*c*-C_6H_{11}	**3c**	O	25	72	**8p** (87)
17	**1a**	H	H	H	**2a**	*c*-C_6H_{11}	**3d**	NH	25	72	**8q** (86)
18	**1b**	H	H	OMe	**2d**	$PhCH_2$	**3d**	NH	25	72	**8r** (30)
19	**1d**	H	Me	H	**2b**	*t*-Bu	**3d**	NH	25	80	**8s** (70)
20	**1c**	H	Cl	H	**2c**	2,6-$Me_2C_6H_3$	**3d**	NH	85	6	**8t** (53)

[a] General procedure: isocyanide **2** (1.1 equiv.) and dienophile **3** (1.1 equiv.) were added under nitrogen to a solution of chromenone **1** (1 equiv.) in THF and stirred at the specified temperature.

[4 + 2] trapping of the 2-aminofuran. Thus a detailed study of the mechanism became necessary in order to both find optimal reaction conditions and broaden the scope of the reaction. Nonetheless, good yields are generally obtained regardless of the nature of these substituents.

Interestingly, the use of non-symmetric dienophiles containing only one electron-withdrawing group (**3e–f**) makes the isolation of the [4 + 1]/[4 + 2] cycloadduct (**7**) prior to aromatization possible (Table 2). Notably, the Diels–Alder reaction was shown to be regioselective, exclusively leading to the 1-hydroxy-1*H*-xanthen-9(2*H*)-ones (**7u–ae**) with the electron-withdrawing group on position C3.[8] The lack of acidic hydrogens on C2 precludes the spontaneous dehydration to aromatic 4-aminoxanthones (**8**), which occurs when the reaction is performed with symmetric dienophiles. This constitutes a remarkably straightforward and efficient route to 1-hydroxy-9-oxo-2,9-dihydro-1*H*-xanthene-1-carboxylates (**7**), which are structurally similar to biologically active globosuxanthones[10] and diversolonic acids.[11] Here again, the reaction was shown to be tolerant of various isocyanides, dienophiles, and substituents on the chromone (Table 2). Additionally, further dehydration of dihydroxanthones (**7**) in the presence of a base such as DBU, cleanly leads to corresponding aromatized xanthones (**8**). These can also be conveniently obtained in a sequential two-step one-pot procedure, as shown in Table 3.

The isolation of 1-hydroxydihydroxanthones (**7u–ae**) strongly supports the initially proposed reaction mechanism involving the sequence of [4 + 1] cycloaddition, iminolactone-aminofuran tautomerization, [4 + 2] cycloaddition, oxygen ring opening and aromatization (Scheme 1). However, again, observing the influence of the chromone substituents on the reaction does not indicate the rate-determining step.

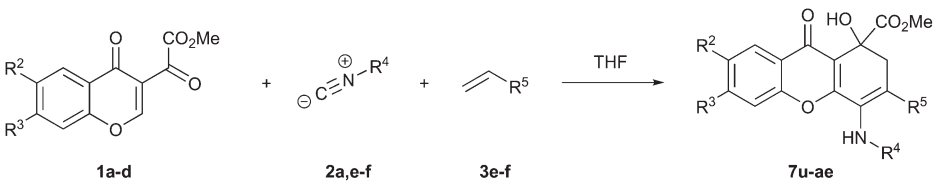
As the synthesis of both xanthones (**8**) and dihydroxanthones (**7**) was successfully carried out from chromones containing electron-donating or electron-withdrawing groups on the aromatic ring, we wondered if the extension of this reaction to 3-carbonylcromones other than 3-methoxalylchromones would be possible. This would allow the formation of xanthones with different substituents on carbon 1. Notably, the substituent on this position seems to be determinant for the biological activity of xanthones.[12]

Accordingly, 3-carbonylchromones containing both electron-withdrawing and electron-donating substituents on the carbonyl group were prepared in order to be used in the synthesis of xanthones. Thus, 3-acetylchromones (**1f**, Y = CH_3) and 3-trifluoroacetylchromones (**1g–h**, Y = CF_3) were readily obtained from (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-ones (**9**) and the corresponding anhydride (**10**), by a modification of Yokoe's method (Scheme 2).[13]

On the other hand, the reaction of 3-(dimethylamino)-1-(2-hydroxyphenyl)propen-1-one (**9**) with *ortho*- or *para*-nitrobezoyl chlorides in Yokoe's conditions always led to mixtures of the desired benzoylchromones and unsubstituted chromones in low yields. Consequently, we developed an alternative synthesis through the Baylis–Hillman (B–H) condensation of chromone (**11**) and the corresponding nitro-substituted benzaldehydes (**12**), followed by oxidation of the resulting alcohols. The B–H reaction was successfully achieved in methanol, using sodium methoxide as a base.[14] The adducts were cleanly oxidised with MnO_2,[15] affording the expected chromones **1i–j** in moderate yields (Scheme 2).

The reaction of these chromones (**1f–j**) with isocyanide (**2a, e–f**) and maleic acid derivatives (**3a–d**) in the conditions previously used with methoxalylchromones was extremely sluggish, and afforded the resulting xanthones (**8**) in poor yields

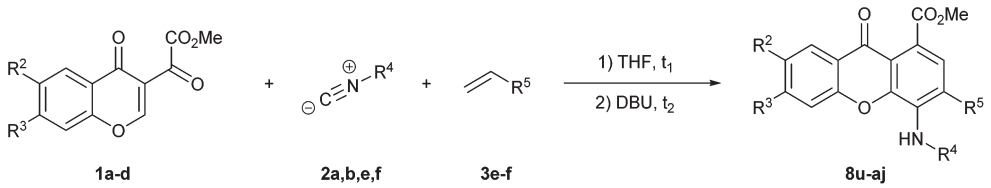
Table 2 Synthesis of 4-amino-1-hydroxydihydroxanthones



Entry	Chromone	R^2	R^3	Isocyanide	R^4	Dienophile	R^5	Time, h	Product (yield, %)
1	**1a**	H	H	**2a**	*c*-C_6H_{11}	**3e**	CN	2	**7u** (81)[a]
2	**1b**	H	OMe	**2a**	*c*-C_6H_{11}	**3e**	CN	4.5	**7v** (82)[a]
3	**1c**	Cl	H	**2a**	*c*-C_6H_{11}	**3e**	CN	2	**7w** (83)[a]
4	**1d**	Me	H	**2a**	*c*-C_6H_{11}	**3e**	CN	2	**7x** (76)[a]
5	**1a**	H	H	**2f**	4-$MeOC_6H_4$	**3e**	CN	9	**7y** (28)[a]
6	**1a**	H	H	**2a**	*c*-C_6H_{11}	**3f**	COMe	0.5	**7z** (70)[b]
7	**1b**	H	OMe	**2a**	*c*-C_6H_{11}	**3f**	COMe	0.5	**7aa** (74)[b]
8	**1c**	Cl	H	**2a**	*c*-C_6H_{11}	**3f**	COMe	1	**7ab** (90)[b]
9	**1d**	Me	H	**2a**	*c*-C_6H_{11}	**3f**	COMe	1	**7ac** (78)[b]
10	**1d**	Me	H	**2f**	4-$MeOC_6H_4$	**3f**	COMe	2	**7ad** (62)[b]
11	**1d**	Me	H	**2e**	C_5H_{11}	**3f**	COMe	1	**7ae** (83)[b]

[a] *Method A*: A solution of **1** (1 equiv.), **2** (1.2 equiv.), and **3e** (2 equiv.) in THF is heated 2–9 h at 70 °C. [b] *Method B*: A solution of **1** (1 equiv.), **2** (1.2 equiv.), and **3f** (1.2 equiv.) in THF is irradiated with MW 0.5–2 h in a close vial at 100 °C.

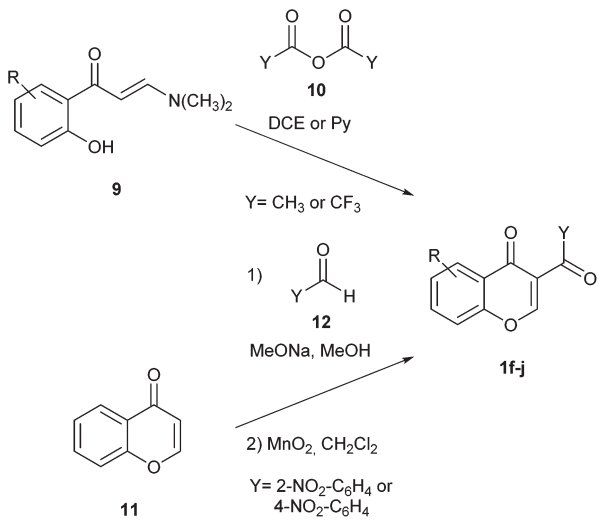
Table 3 One-pot synthesis of xanthones (**8**) from asymmetric dienophiles (**3e–f**)



1a-d **2a,b,e,f** **3e-f** **8u-aj**

Entry	Chromone	R^2	R^3	Isocyanide	R^4	Dienophile	R^5	t_1/t_2, h	Product (yield, %)
1	**1a**	H	H	**2a**	*c*-C_6H_{11}	**3e**	CN	2/0.5	**8u** (78)[a]
2	**1a**	H	H	**2a**	*c*-C_6H_{11}	**3e**	CN	0.5/0.2	**8u** (75)[b]
3	**1b**	H	OMe	**2a**	*c*-C_6H_{11}	**3e**	CN	9/1	**8v** (65)[a]
4	**1c**	Cl	H	**2a**	*c*-C_6H_{11}	**3e**	CN	2.5/0.5	**8w** (70)[a]
5	**1d**	Me	H	**2a**	*c*-C_6H_{11}	**3e**	CN	5/1.5	**8x** (68)[a]
6	**1a**	H	H	**2a**	*c*-C_6H_{11}	**3f**	COMe	0.5/1	**8z** (76)[b]
7	**1b**	H	OMe	**2a**	*c*-C_6H_{11}	**3f**	COMe	1/1.5	**8aa** (75)[b]
8	**1c**	Cl	H	**2a**	*c*-C_6H_{11}	**3f**	COMe	1/0.3	**8ab** (68)[b]
9	**1d**	Me	H	**2a**	*c*-C_6H_{11}	**3f**	COMe	6.5/1	**8ac** (70)[b]
10	**1d**	Me	H	**2f**	4-$MeOC_6H_4$	**3f**	COMe	3/0.5	**8ad** (70)[b]
11	**1d**	Me	H	**2e**	C_5H_{11}	**3f**	COMe	1.5/1	**8ae** (44)[b]
12	**1b**	H	OMe	**2b**	*t*-Bu	**3e**	CN	3/0.5	**8af** (69)[a]
13	**1b**	H	OMe	**2b**	*t*-Bu	**3e**	CN	1/0.2	**8af** (69)[b]
14	**1c**	Cl	H	**2b**	*t*-Bu	**3e**	CN	3.5/0.5	**8ag** (78)[a]
15	**1b**	H	OMe	**2f**	4-$MeOC_6H_4$	**3e**	CN	3/0.5	**8ah** (40)[a]
16	**1c**	Cl	H	**2f**	4-$MeOC_6H_4$	**3e**	CN	8/0.5	**8ai** (27)[a]
17	**1c**	Cl	H	**2e**	C_5H_{11}	**3f**	COMe	0.5/0.5	**8aj** (48)[b]

[a] *Method A*: A solution of **1** (1 equiv.), **2** (1.2 equiv.), and **3e** (2 equiv.) was heated in THF at 70 °C for 2–9 h before the addition of 2 equiv. DBU and further heating of the reaction mixture for 25–75 min at the same temperature. [b] *Method B*: A solution of **1** (1 equiv.), **2** (1.2 equiv.), and **3f** (1.2 equiv.) in THF was irradiated with MW in a sealed vial at 100 °C for 0.5–6 h. Then DBU (2 equiv.) was added and the reaction mixture was further irradiated of for 10–90 min.



Scheme 2 Synthesis of 3-carbonylchromones.

(Table 4, entries 1, 5, 7, 12, 16 and 20). However, increasing the reaction temperature to 80 °C affords the corresponding 4-aminoxanthones **8ak–ax** in moderate to excellent yields in a reasonable reaction time (Table 4).

Thus, the reaction with acetylchromone (**1f**) requires 40 hours to complete. As expected, the reaction times with more electron-poor chromones (**1g–j**) are significantly shorter. Accordingly, the reaction with trifluoroacetylchromones (**1g–h**; Table 4, entries 6, 8–11) and *ortho*-nitrobenzoylchromone (**1i**; Table 4, entries 13–15) is typically completed in less than 30 h. Intermediate reaction times were observed when *para*-nitrobenzoylchromone (**1j**) was used (Table 4, entries 17–19, 21–22).

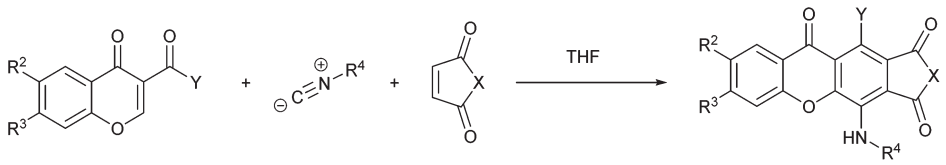
In an attempt to reduce the reaction times, the possible catalytic effect of Lewis acids was explored. However, the addition of either yttrium triflate or lithium perchlorate to the reaction mixture led to longer reaction times (Table 4, entries 3 and 4).

The previous results demonstrate that the reaction is equally feasible with 3-carbonylchromones containing both electron-withdrawing and electron-donating substituents on the carbonyl group. Additionally, different dienophiles and isocyanides can also be used. Moreover, the data above indicate that increasing the reaction temperature allows to readily reach the activation energy, resulting in high yields and increased reaction rates. However, puzzlingly, there does not seem to be a clear influence of the electronic nature of the starting chromone on either the yields or the reaction times.

As expected, the 3-component reaction of chromones **1g,h,j**, isocyanide **2a** and asymmetric dienophiles **3e,f**, carried out at 100 °C, affords regioselectively the xanthones (**8ay–ba**) with no substituent in position 3 (Table 5).

Going a step forward, as the absence of an electron group attached to the carbonyl group of 3-carbonylchromones does not seem to drastically affect their reactivity, we considered

Table 4 3-Component reactions of chromones **1f–j** with isocyanides and maleic acid derivatives

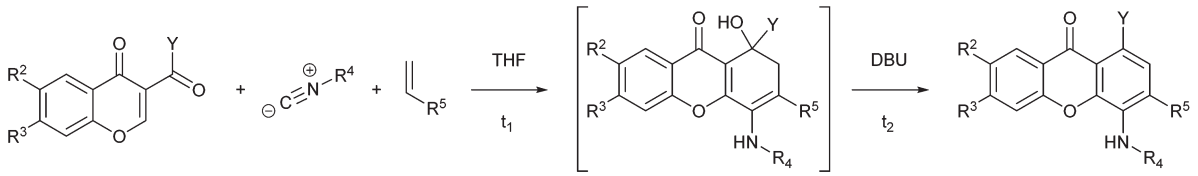


1f-j **2a,e-f** **3a-d** **8ak-ax**

Entry	Chromone	R^2	R^3	Y	Isocyanide	R^4	Dienophile	X	*T*, °C	Time	Product (yield, %)
1	**1f**	H	H	CH_3	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	35	14 d	**8ak** (39)
2	**1f**	H	H	CH_3	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	80	40 h	**8ak** (95)
3	**1f**	H	H	CH_3	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	80	>7.5 d	**8ak** (IR)[a,b]
4	**1f**	H	H	CH_3	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	80	68 h	**8ak** (95)[c]
5	**1g**	H	H	CF_3	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	35	8 d	**8al** (31)
6	**1g**	H	H	CF_3	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	80	21 h	**8al** (61)
7	**1h**	H	OMe	CF_3	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	35	14 d	**8am** (29)
8	**1h**	H	OMe	CF_3	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	80	13 h	**8am** (58)
9	**1g**	H	H	CF_3	**2a**	*c*-C_6H_{11}	**3b**	*N*-CH_3	80	17 h	**8an** (26)
10	**1h**	H	OMe	CF_3	**2a**	*c*-C_6H_{11}	**3b**	*N*-CH_3	80	31 h	**8ao** (59)
11	**1g**	H	H	CF_3	**2f**	4-$MeOC_6H_4$	**3bf**	*N*-CH_3	80	31 h	**8ap** (53)
12	**1i**	H	H	*o*-NO_2Ph	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	35	6 d	**8aq** (67)
13	**1i**	H	H	*o*-NO_2Ph	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	80	7 h	**8aq** (77)
14	**1i**	H	H	*o*-NO_2Ph	**2a**	*c*-C_6H_{11}	**3d**	*N*-H	80	31 h	**8ar** (37)
15	**1i**	H	H	*o*-NO_2Ph	**2a**	*c*-C_6H_{11}	**3c**	O	80	22 h	**8as** (88)
16	**1j**	H	H	*p*-NO_2Ph	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	35	16 d	**8at** (IR)[b]
17	**1j**	H	H	*p*-NO_2Ph	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	80	35 h	**8at** (93)
18	**1j**	H	H	*p*-NO_2Ph	**2e**	C_5H_{11}	**3b**	*N*-CH_3	80	20 h	**8au** (68)
19	**1j**	H	H	*p*-NO_2Ph	**2e**	C_5H_{11}	**3d**	*N*-H	80	5 d	**8av** (66)
20	**1j**	H	H	*p*-NO_2Ph	**2e**	C_5H_{11}	**3c**	O	35	16 d	**8aw** (IR)[b]
21	**1j**	H	H	*p*-NO_2Ph	**2e**	C_5H_{11}	**3c**	O	80	5 d	**8aw** (59)
22	**1j**	H	H	*p*-NO_2Ph	**2f**	4-$MeOC_6H_4$	**3a**	*N*-Ph	80	6 d	**8ax** (51)

[a] The experiment was made with 5% of yttrium triflate. [b] IR: incomplete reaction. [c] The experiment was made with 7% of lithium perchlorate.

Table 5 Reactions of chromones **1g,h,j** with asymmetric dienophiles



1g,h,j **2a** **3e-f** **7ay-ba** **8ay-ba**

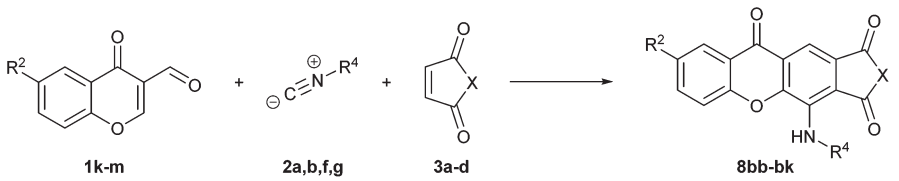
Entry	Chromone	R^2	R^3	Y	Isocyanide	R^4	Dienophile	R^5	*T*, °C	t_1, h	t_2, min	Product (% yield)[a]
1	**1g**	H	H	CF_3	**2a**	*c*-C_6H_{11}	**3e**	CN	100	2	20	**8ay** (28)
2	**1h**	H	OMe	CF_3	**2a**	*c*-C_6H_{11}	**3f**	COMe	100	2	30	**8az** (41)
3	**1j**	H	H	*p*-NO_2Ph	**2a**	*c*-C_6H_{11}	**3e**	CN	100	5	15	**8ba** (56)

[a] General procedure: a solution of **1** (1 equiv.), **2a** (1.2 equiv.), and **3e** (2 equiv.) or **3f** (1.2 equiv.) in THF was irradiated with MW in a sealed vial at 100 °C for 2–5 h. Then DBU (2 equiv.) was added and the reaction mixture was further irradiated of for 15–30 min.

using 3-formylchromones as starting materials in the synthesis of xanthones.[16,17] This provides two advantages: 3-formylchromones are readily available and the resulting xanthones that are unsusbstituted on position 1 could be easily transformed into other xanthones of biological interest.

The reaction of 3-formylchromone (**1k**) with cyclohexyl isocyanide (**2a**) and *N*-phenylmaleimide (**3a**) in THF proceeds quite slowly, even at refluxing temperature (Table 6, entries 1 and 2). Thus, in order to find better reaction conditions, we tried different solvents and temperatures (Table 6). To our delight, when the reaction was performed in refluxing toluene for 41 hours, the expected xanthone **8bb** was obtained in 89% yield (Table 6, entry 3). The structure was confirmed by the usual spectroscopic data. Significantly, ^{1}H-NMR of **8bb** shows a singlet at 8.11 ppm, corresponding to the characteristic aromatic hydrogen in position 4 of the xanthone.

Table 6 Reactions of 3-formylchromones with isocyanides and dienophiles[a]



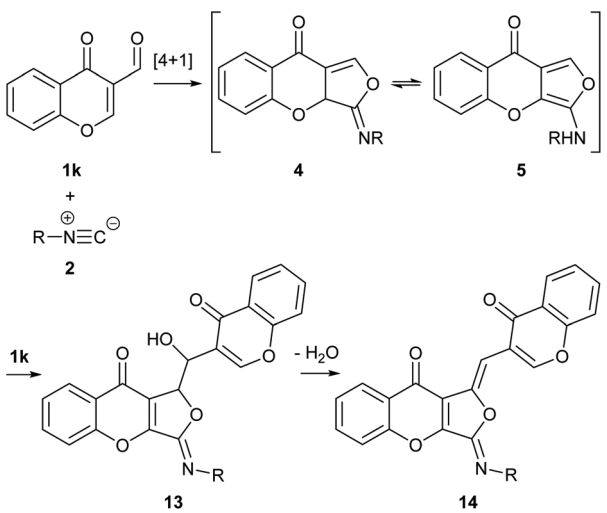
Entry	Chromone	R^2	R^3	Isocyanide	R^4	Dienophile	X	*T*, °C	Solvent	Time, h	Product (yield, %)
1	**1k**	H	H	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	35	THF	168	**8bb** (IR)[b]
2	**1k**	H	H	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	80	THF	107	**8bb** (71)
3	**1k**	H	H	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	110	Toluene	41	**8bb** (89)
4	**1k**	H	H	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	110	Toluene	11	**8bb** (CM)[c,d]
5	**1k**	H	H	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	110	Toluene	26	**8bb** (44)[e]
6	**1k**	H	H	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	110	Dioxane	68	**8bb** (90)
7	**1k**	H	H	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	150	Dibutylether	44	**8bb** (88)
8	**1l**	Cl	H	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	110	Toluene	25	**8bc** (92)
9	**1m**	Me	H	**2a**	*c*-C_6H_{11}	**3a**	*N*-Ph	110	Toluene	60	**8bd** (87)
10	**1m**	Me	H	**2a**	*c*-C_6H_{11}	**3d**	*N*-H	110	Toluene	48	**8be** (87)
11	**1m**	Me	H	**2a**	*c*-C_6H_{11}	**3b**	*N*-CH_3	110	Toluene	59	**8bf** (70)
12	**1m**	Me	H	**2a**	*c*-C_6H_{11}	**3c**	O	110	Toluene	62	**8bg** (46)
13	**1k**	H	H	**2b**	*t*-Bu	**3a**	*N*-Ph	110	Toluene	124	**8bh** (58)
14	**1m**	Me	H	**2b**	*t*-Bu	**3a**	*N*-Ph	110	Toluene	29	**8bi** (33)
15	**1k**	H	H	**2f**	4-$MeOC_6H_4$	**3a**	*N*-Ph	110	Toluene	41	**8bj** (42)
16	**1k**	H	H	**2g**	CH_2CO_2t-Bu	**3a**	*N*-Ph	110	Toluene	95	**8bk** (85)
17	**1k**	H	H	**2b**	*t*-Bu	**3a**	*N*-Ph	35	DCM	360	**8bh** (67, IR)[b,17]
18	**1k**	H	H	**2b**	*t*-Bu	**3c**	O	35	DCM	360	**8bl** (33, IR)[b,17]

[a] General procedure: Isocyanide **2** (1.2 equiv.) and dienophile **3** (1.2 equiv.) were added under nitrogen to a solution of chromenone **1** (1 equiv.) in the specified solvent and stirred at the specified temperature. [b] IR: the reaction did not reach completion and a mixture of starting materials and product was obtained. [c] CM: complex mixture. [d] $AlCl_3$ (5%mol). [e] $Y(OTf)_3$ (5%mol).

The use of catalytic Lewis acids such as $AlCl_3$ and $Y(OTf)_3$ (Table 6, entries 4 and 5), does not improve the performance of the reaction. Despite the increased reaction rate, several side products are formed, the work up and isolation of the product is complex and tedious, and the resulting yield is lower.

The optimized reaction conditions were applied to other combinations of commercially available formylchromones (**1k–m**), maleimide derivatives (**3a–d**) and isocyanides (**2a–g**) (Table 6, entries 8–18). The process gave moderate to excellent yields and was shown to be tolerant to different isocyanides, dienophiles, and substituents on the chromone. As previously noted with chrome **1a**, less hindered cyclohexyl or $CH_2CO_2{}^tBu$ isocyanide gave better results in the tandem reaction than *tert*-butyl isocyanide, which took 5 days to complete in refluxing toluene.

In a previous work, we have shown that 3-formylchromones react with isocyanides to give chromenylmethylene furochromenones (**14**), purportedly through a 2-aminofuran intermediate (**5**; Scheme 3).[18] This reaction takes just 5 to 8 hours in refluxing THF, in contrast with the unexpectedly slow reaction of 3-formylchromones, isocyanides and dienophiles, which was supposed to occur through the same 2-aminofuran intermediate (**4**). Obviously, this suggests that either the [4 + 1] cycloaddition leading to 2-aminofuran (**5**) is not the rate determining step of the synthesis of xanthones (**8**; Scheme 1), or the mechanism for the synthesis of **14** outlined in Scheme 3 is not valid.



Scheme 3 Proposed mechanism for the reaction of formylchromones and isocyanides.[18]

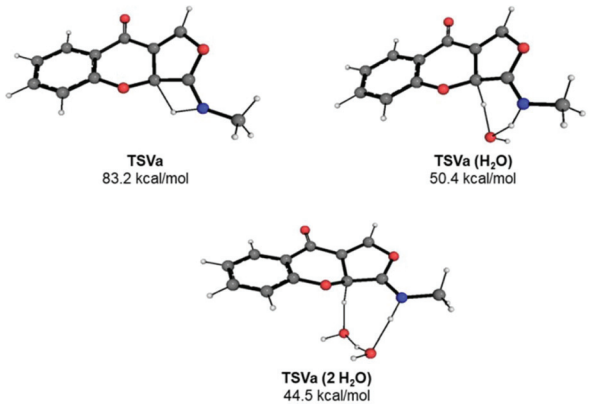
DFT calculations

In an attempt to explain the lack of consistency between the experimental results and our initial mechanistic hypothesis of a slow [4 + 1] cycloaddition leading to iminolactone (**4**), followed by a rapid tautomerization and [4 + 2] trapping of the 2-aminofuran (**5**), we decided to carry out a computational

study of all the reactants, products, and transition states. With this aim, density functional theory (DFT) calculations were performed with Gaussian 16. The geometries of the reactants, products, intermediates, and transition states (TS) involved in this mechanistic study were fully optimized in both THF and toluene with the Polarizable Continuum Model (PCM) at the B3LYP/6-31+G* level of theory. The reaction was initially modelled with 3-formylchromone (**I**, **1k**), methyl isocyanide (**II**) and *N*-methylmaleimide (**3b**) in THF (Scheme 4). The reliability of the method and basis set used was further confirmed with calculations at the PCM-M06-2X/6-31+G** level in Gaussian 09 (see ESI Table S5†).

The computational data reveals that the driving force of the reaction is undoubtedly the thermodynamic stability of the final xanthone (**VII**), with an energy value 43 kcal mol^{-1} lower than the initial multicomponent precursors. According to the proposed mechanism, 3-carbonyl chromone (**I**) and isocyanide (**II**) react to produce the intermediate iminolactone (**IVa**), which is 8.5 kcal mol^{-1} less stable than the reactants (Scheme 4). In congruence with previous studies,[19] we found that this step proceeds through a [4 + 1] stepwise cycloaddition, in which an activation energy of 30 kcal mol^{-1} must be overcome to reach a first zwiterionic intermediate (**III**). This intermediate quickly reacts, crossing a small energy barrier of 2.5 kcal mol^{-1}, to form the iminolactone ring (**IVa**).

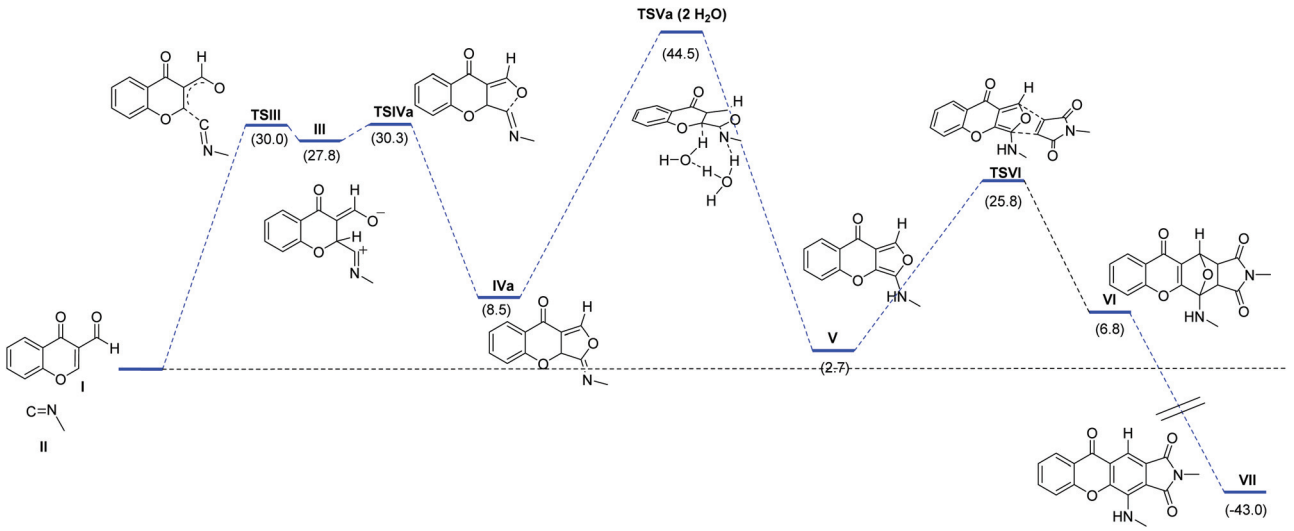
To our surprise, tautomerization of the iminolactone (**IVa**) to the aminofuran (**V**) was shown to be a high-energy cost process, which should reach a TS (**TSVa**) of 83.2 kcal mol^{-1} (see ESI†). In order for this process to be feasible, either solvents or other molecules should necessarily participate in the transition state. Water released in the final dehydration step may assist the hydrogen shift process affording aminofuran (**V**). There is evidence that other similar tautomerism processes are assisted by either water or other solvent molecules.[20] Indeed, the inclusion of one or two molecules of water in the calculations leads to much lower transition states (**TSVa (H_2O)** and **TSVa ($2H_2O$)**; Scheme 5) of 50.4 and 44.5 kcal mol^{-1}, respectively. However, the activation barrier for the tautomerization step is still 36 kcal mol^{-1}. This makes the tautomerization the rate limiting step of the overall process, and explains why heating is required for this reaction.



Scheme 5 Calculated TS for the iminolactone-aminofuran tautomerization, without and with the participation of water molecules.

We found an energy barrier of 23.1 kcal mol^{-1} for the [4 + 2] cycloaddition of the aminofuran (**V**) and *N*-methylmaleimide (**3b**), which is considerably lower than that found for the iminolactone-aminofuran tautomerization (Tables 7 and 8). Finally, all the attempts to find TSs for the opening of the oxygen bridge and dehydration steps were unsuccessful. These two transformations likely have low energy barriers and take place quite quickly due to the much higher stability of the final xanthone (**VII**). Calculations using toluene instead of THF gave similar energy values (Table 7).

An alternative pathway for the transformation of zwitterionic intermediate **III** into aminofuran **V** can also be envi-



Scheme 4 Reaction profile for the multicomponent synthesis of xanthones (**8**), calculated at B3LYP/6-31+G* level of theory.

Table 7 Energies of the principal transition states and intermediates calculated at B3LYP/6-31+G* level of theory[a]

Chromone (**I**) & methyl isocyanide (**II**)	TS_{III}	Zwiterion (**III**)	TS_{IVa}	Iminolactone (**IVa**)	TS_{Va} ($2H_2O$)	Aminofuran (**V**)	TS_{VI}	Xanthone (**VII**)
1k (THF)	30.03	27.76	30.33	8.54	44.54	2.68	25.76	−42.96
1k (toluene)	31.14	30.24	32.29	7.13	41.56	1.05	25.22	−43.97
1a	28.10	25.18	32.26	14.64	42.07	3.76	38.51	−35.65
1i	30.54	26.15	28.89	7.04	42.09	−0.26	33.00	−36.43
1j	30.21	27.11	29.62	4.24	39.48	−5.92	27.91	−36.38

[a] Calculations were fully performed with Gaussian 16.

Table 8 Calculated energy barriers including the temperature thermodynamic effect

	Room temperature				Real temperature of reaction			
Chromone	Δ(TS_{III}-**I** & (**II**)) [4 + 1] step 1	Δ(TS_{IVa}-**III**) [4 + 1] step 2	Δ(TS_{Va}-**IVa**) tautomerization	Δ(TS_{VI}-**V**) Diels–Alder	Δ(TS_{III}-**I&II**) [4 + 1] step 1	Δ(TS_{IVa}-**III**) [4 + 1] step 2	Δ(TS_{Va}-**IVa**) tautomerization	Δ(TS_{VI}-**V**) Diels–Alder
1k (THF)	30.03	2.56	36.01	23.08	31.51	2.73	38.92	24.84
1k (toluene)	31.14	2.05	34.42	24.17	34.25	2.53	40.50	28.01
1a	28.10	7.08	27.43	34.74	28.10	7.08	27.43	34.74
1i	30.54	2.75	35.06	33.26	32.01	2.97	37.97	35.25
1j	30.21	2.51	35.24	33.84	31.71	2.82	38.18	35.80

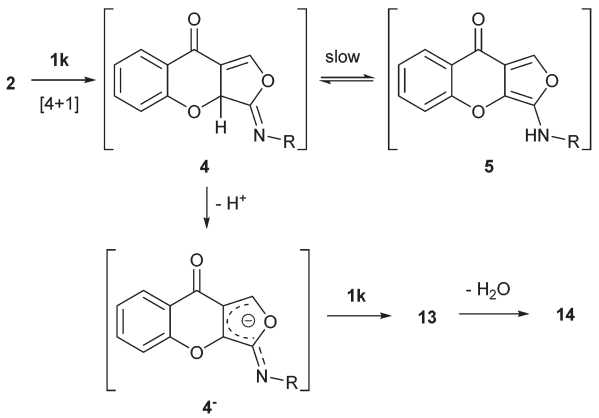
sioned, considering the direct abstraction of the hydrogen in chromone position 2 by the carbonylic oxygen (see ESI Mechanism B, Scheme S1 and Table S2†). DFT calculations show that this alternative mechanism requires overcoming a maximum energy barrier (**TSIVb**) of 48.3 kcal mol^{-1}, which is significantly higher than the 44.5 kcal mol^{-1} corresponding to the higher energy transition state (**TSVa ($2H_2O$)**) in the first proposed mechanism (see ESI†). Calculations also show that this alternative **TSIVb** is not stabilized by water. Thus, the reaction most probably occurs through the stepwise [4 + 1] cycloaddition leading to iminolactone **IVa**, followed by water-facilitated tautomerization to aminofuran **V**. Moreover, there are strong experimental evidences that support the mechanism *via* the iminolactone-aminofuran tautomerization. These include the isolation of related iminolactones reported in the literature[21] and the influence of added water in the reaction rate (see below).

We also performed calculations with chromones substituted with CO_2Me (**1a**), *o*-nitrophenyl (**1i**) and *p*-nitrophenyl (**1j**) on the carbonyl group (Tables 7 and 8). The reaction coordinates are similar for each of the four examples. The activation energies for the [4 + 1] and [4 + 2] reactions are moderate in each case, between 23–35 kcal mol^{-1}. The energy barrier for the [4 + 1] cycloaddition is almost independent of the nature of the substituent on the carbonyl group. On the contrary, the presence of electro-withdrawing groups in **1a,i–j** results in significantly higher activation energies for the Diels–Alder reaction (Tables 7 and 8).

The iminolactone-aminofuran tautomerization is the slowest step in most of the cases, with energy barriers around 35 kcal mol^{-1}. An exception is the reaction with chromone **1a**, in which intermediate **IVa** is destabilized by the substituent CO_2Me being out of the plane of the molecule. Also, the strong electron-withdrawing character of the substituent CO_2Me enhances the acidity of the hydrogen α to the imine group in **IVa**, facilitating the tautomerization. As a result, the activation energy is only 27.4 kcal mol^{-1}, significantly lower than the barrier corresponding to the [4 + 2] cycloaddition. This is in accordance with the experimental results, which demonstrate that the reaction with chromone **1a** can take place at lower temperature, between 25–35 °C. Furthermore, experimental results with substituted methoxalylchromones (**1a–e**; Table 1) show that electron-donating substituents on the aromatic ring of the starting chromone seem to favor the reaction, which is consistent with the rate-determining step being the [4 + 2] cycloaddition in this case.

Table 8 summarizes the activation energies required to reach each of the successive transition states, including the temperature thermodynamic effect. The calculations show that, although aminofuran (**V**) is more stable in each case than its iminolactone counterpart (**IVa**), their interconversion requires the assistance of water and it is still a rather slow process. Tautomerization is thus the rate determining step in all the cases, except for the reactions with methoxalylchromone (**1a**).

On the other hand, a new rationale should be determined for the synthesis of furochromones (**14**), as the mechanism showed in Scheme 3 is not compatible with the relatively short reaction times observed, considering the high energy barriers for the aminolactone-aminofuran tautomerization.[18] The formation of furochromones (**14**) can thus be explained by a vinylogous aldol addition[22] of a second chromone molecule on the iminolactone (**4**), which implies that the aminofuran (**5**) does not even form (Scheme 6; *cf.* Scheme 3). The reaction may be



Scheme 6 Mechanism for the synthesis of chromenylmethylene furochromenones (**14**), based on computational studies.

catalyzed by external bases, such as water molecules or any products or intermediates containing basic nitrogen atoms present in the reaction medium. Abstraction of the proton on C-3 of iminolactones and the subsequent addition of electrophiles to C-5 in the presence of catalytic Lewis acid has been reported by Chatani and co-workers.[21a]

In congruence with theoretical calculations, the addition of water to the reaction medium should facilitate the tautomerization reaction, speeding up the whole process. To probe this hypothesis, we performed some experiments in which 8 equivalents of water was added to the reaction of fomylchromones (**1k,m**), isocyanides (**2a,b**), and *N*-phenylmalimide (**3a**), either in THF or toluene. As expected, the reactions were significantly quicker, but lower yields were usually obtained. This could be attributed to the formation of side products, as observed on tlc, and a consequent more complicated work up and purification (Table 9; *cf.* Table 6). Thus, xanthone **8bb** was obtained in only 6 h in refluxing toluene (Table 9, entry 1), compared to the 41 h required in anhydrous conditions (Table 6, entry 3). However, the yield was reduced from 89% in anhydrous conditions to 63% in the presence of water. Analogously, in THF, the addition of water reduced the reaction time from 107 (Table 6, entry 2) to 6 hours (Table 9, entry 2), and slightly lowered the yield from 71% to 69%. Similar results were observed for the synthesis of xanthones **8bd** (Table 6, entry 9 and Table 9, entry 3) and **8bh** (Table 6, entry 13 and Table 9, entry 4).

In order to evaluate the multicomponent synthesis of xanthones toward the construction of more complex and naturally occurring xanthone scaffolds, dimeric dihydroxanthone **18**[8] and xanthone **19** were readily synthesized from commercially available bisphenol (**15**). The common precursor bischromone **17** was obtained by acetylation, acid catalyzed Fries rearrangement,[23] aldol condensation with dimethylformamide dimethyl acetal and cyclization in the presence of 2-chloro-2-oxoacetate (Scheme 7).

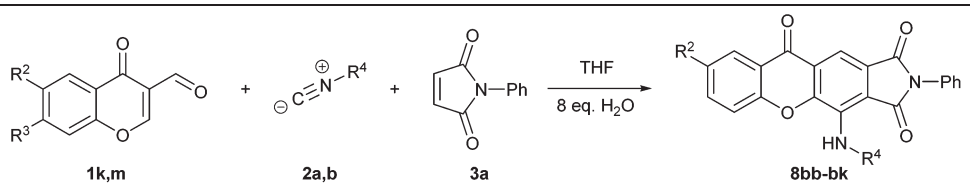
The reaction of bischromone **17**, cyclohexyl isocyanide (**2a**), and acrylonitrile (**3e**) under reflux in toluene successfully afforded dihydroxanthone **18** with a 55% yield over three steps.[8] Similarly, when *N*-phenylmaleimide (**3a**) was substituted for acrylonitrile (**3e**), xanthone **19** was obtained with a 79% yield (Scheme 7).

Interestingly, the new xanthones could be further transformed into other polyheterocyclic molecules of biological interest. For example, 1-aryl-substituted xanthones could be useful intermediates for the synthesis of chromenophenantridines, which are interesting materials for organic electronic applications[24] and have shown high efficacy in tumor cell growth inhibition due to their telomeric DNA G-quadruplex binding properties.[25]

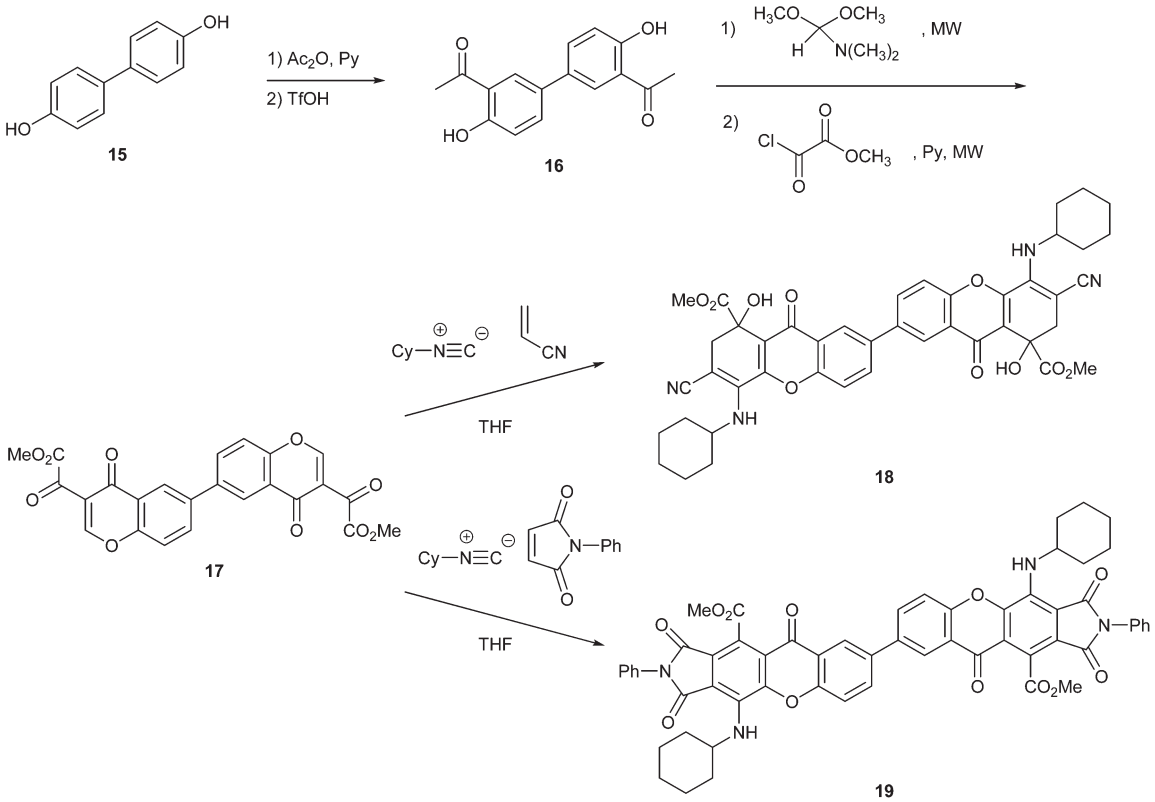
Therefore, 1-(*ortho*-nitrophenyl)xanthones **8aq–as** were readily reduced and cyclized with iron in acetic acid at 130 °C to give phenanthridine derivatives **20aq–as** (Scheme 8).

These phenantridines were highly intense red fluorescent, in contrast to precursor xanthones, which show yellow fluorescence. They show distinctive IR bands at *ca.* 1700 and 1750 cm^{-1} (**20aq**, **20ar**) or 1740 and 1800 cm^{-1} (**20as**), characteristic of maleimides and maleic anhydrides, respectively. This supports that cyclization of the intermediate aniline takes place through the carbonyl of the chromone, and the maleic moiety remains unchanged. This was also confirmed by the loss in **20aq** of the ^{13}C-NMR signal at 180 ppm corresponding to the chromone carbonyl in the starting material.

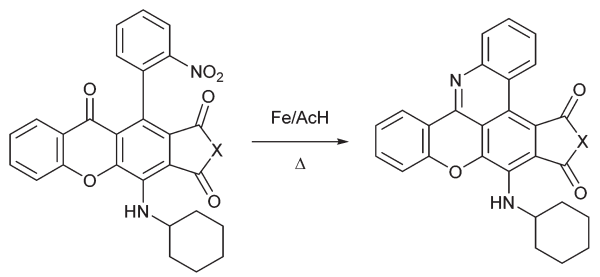
Table 9 Synthesis of xanthones **8** in the presence of added water



Entry	Chromone	R^2	R^3	Isocyanide	R^4	*T*, °C	Solvent	Time, h	Product (yield, %)
1	**1k**	H	H	**2a**	*c*-C_6H_{11}	110	Toluene	6	**8bb** (63)
2	**1k**	H	H	**2a**	*c*-C_6H_{11}	80	THF	6	**8bb** (69)
3	**1m**	Me	H	**2a**	*c*-C_6H_{11}	80	THF	5	**8bd** (67)
4	**1k**	H	H	**2b**	*t*Bu	80	THF	5	**8bh** (50)



Scheme 7 Synthesis of dimeric xanthones **18** and **19**.



Scheme 8 Synthesis of phenanthridines.

Conclusions

In conclusion, we have successfully designed a straightforward multicomponent synthesis of xanthones and dihydroxanthones. The highly convergent and atom economic process takes place in one-pot, in very mild conditions and with no need of catalysts. Theoretical calculations demonstrate that the reaction occurs as an ordered sequence of a [4 + 1] stepwise cycloaddition, iminolactone-aminofuran tautomerization, [4 + 2] cycloaddition, oxygen ring opening and aromatization. Tautomerization is the rate-limiting step, and it has been shown to be possible only in the presence of water that participates in the transition state facilitating the hydrogen shift process. Accordingly, water was experimentally shown to significantly increase the rate of the reaction.

We have demonstrated the utility of this methodology for the synthesis of biologically relevant chromenophenantridines and dimeric xanthones and dihydroxanthones structurally related to secalonic acid. These compounds, that otherwise require long and complex syntheses, can be straightforwardly obtained with high yields and selectivity.

Experimental section

Computational details

Quantum chemical computations were carried out with the Gaussian 16 series of programs.[26] Full geometry optimizations of stable species were performed in the appropriate solvent by employing the hybrid density functional B3LYP[27] with the 6-31+G(d) basis set.[28] The B3LYP functional combines the Becke's three-parameter nonlocal hybrid exchange potential with the nonlocal correlation functional of Lee, Yang, and Parr. The nature of the stationary points was verified by analytical computations of harmonic vibrational frequencies. The reliability of the calculations were performed at M06-2X[29] with the 6-31+G(d,p) basis set. Solvent effects were considered using the integral equation formalism variant of the polarizable continuum model (IEF-PCM) with the Polarizable Continuum Model (PCM).[30]

Synthesis of chromones (1f–1j)

3-Acetyl-4*H*-chromen-4-one (1f).[31] A solution of (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one **9a** (214 mg, 1.16 mmol) in pyridine (1 mL) and two drops of piperidine was cooled in an ice-bath and then acetic anhydride **10a** (1 mL, 9 mmol) was added dropwise. The reaction was let to slowly reach the room temperature overnight and then it was heated at 120 °C until the starting material was consumed (2 hours). The residue was washed with saturated aqueous brine (3 × 15 mL) and $CuSO_4$ (3 × 15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was dried over Na_2SO_4 and concentrated, and the crude was purified by column chromatography (silica gel, hexane–EtOAc gradient), giving the desired chromone **1f** (129 mg, 59%), obtained as a white solid; mp: 128–132 °C (lit.[31] 125–128 °C).

3-(2-Nitrobenzoyl)-4*H*-chromen-4-one (1i).[32] To a solution of 4*H*-chromen-4-one **11** (184 mg, 1.25 mmol) and *o*-nitrobenzaldehyde **12a** (158 mg, 1 mmol) in dry methanol (0.5 mL), sodium *tert*-butoxide (27 mg, 0.267 mmol) in methanol (2.5 mL) was added dropwise under a nitrogen atmosphere. Once the chromone **11** was consumed (72 hours), a solution of HCl 1N (2 mL) was added to the reaction mixture. The solvents were removed in the rotary evaporator, and the residue was redissolved in ethyl acetate and washed with H_2O (3 × 15 mL). The organic phase was dried over Na_2SO_4 and concentrated, and the resulting solid was washed with methanol and ethyl acetate, giving the Baylis–Hillman intermediate 3-(hydroxy(2-nitrophenyl)methyl)-4*H*-chromen-4-one (196 mg, 66%), as a white solid.

A solution of 3-(hydroxy(2-nitrophenyl)methyl)-4*H*-chromen-4-one (96 mg, 0.38 mmol) and MnO_2 (667 mg, 7.7 mmol) in CH_2Cl_2 (6 mL) was stirred at room temperature under a nitrogen atmosphere until the starting material was consumed (1.25 hours). Then the mixture was filtered over Celite, washing with CH_2Cl_2 (20 mL), and the organic residue was evaporated, giving a white solid, which was washed with cyclohexane affording **1i** (103 mg, 92%).

General procedure for the synthesis of xanthones (8a–bk)

Isocyanide **2a–g** (1.2 mmol) and dienophile **3a–f** (1.2 mmol) are successively added to a solution of chromenone **1a–m** (1 mmol) in the appropriate solvent (2 mL). The resulting mixture is stirred at the appropriate temperature under a nitrogen atmosphere until the chromone (**1**) is consumed. HCl 1 N (2 mL) is then added to the reaction mixture, and after 30 minutes, the crude is washed with brine (15 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The organic phase is dried over Na_2SO_4 and concentrated. The resulting residue is purified by column chromatography (silica gel, hexane–EtOAc gradient), giving the desired product **8**.

4-(Cyclohexylamino)-11-methyl-2-phenylchromeno[2,3-*f*]isoindole-1,3,10(2*H*)-trione (8ak). Obtained as a yellow solid (95% yield); mp: 214 °C; IR (cm^{-1}): 3430, 2922, 2853, 1754, 1694, 1656, 1611; ^1H NMR (500 MHz, $CDCl_3$): δ 8.28 (d, J = 8.0 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.53–7.50 (m, 2H), 7.45–7.39 (m, 5H), 6.77 (bs, 1H, NH), 4.27 (m, 1H), 3.19 (s, 3H), 2.13 (m, 2H), 1.84 (m, 2H), 1.67–1.25 (m, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 178.8 (C), 168.3 (C), 167.1 (C), 154.5 (C), 151.7 (C), 137.1 (C), 135.1 (CH), 131.8 (C), 131.6 (C), 129.1 (CH), 128.8 (CH), 128.3 (CH), 127.1 (CH), 126.8 (CH), 125.3 (CH), 125.0 (C), 123.0 (C), 122.6 (C), 117.3 (CH), 114.2 (C), 54.6 (CH), 34.9 (CH_2), 25.8 (CH_2), 24.9 (CH_2), 15.9 (CH_3) ppm; MS (CI) m/z (%) 453 (M + 1, 39), 452 (M^+, 13), 375 (22), 347 (93), 298 (100); HRMS (EI) Calcd for $C_{28}H_{24}N_2O_4$: 452.17361. Found: 452.1735.

Dimethyl 4,4′-bis(cyclohexylamino)-1,1′,3,3′,10,10′-hexaoxo-2,2′-diphenyl-1,1′,2,2′,3,3′,10,10′-octahydro-[8,8′-bichromeno[2,3-*f*]isoindole]-11,11′-dicarboxylate (19). Obtained as a yellow solid (79%); mp: 355 °C (dec); IR (cm^{-1}): 3455, 2929, 1762, 1701, 1664, 1614; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 2H), 8.01 (d, J = 7.9 Hz, 2H), 7.59–7.42 (m, 11H), 6.78 (s, 2H), 4.34 (s, 2H), 4.18 (s, 6H), 4.12 (s, 1H), 2.15–1.30 (m, 20H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): 175.1 (C), 167.7 (C), 166.8 (C), 164.7 (C), 154.2 (C), 148.8 (C), 138.7 (C), 136.2 (C), 134.4 (CH), 131.4 (C), 129.3 (CH), 128.4 (CH), 126.6 (CH), 124.2 (CH), 123.7 (C), 122.4 (C), 121.3 (C), 119.3 (CH), 118.2 (C), 112.6 (C), 54.4 (CH), 53.4 (CH_3), 34.4 (CH_2), 25.6 (CH_2), 24.5 (CH_2) ppm; HRMS (ESI-ICP-Q-TOF) Calcd for $C_{58}H_{46}N_4O_{12}$ H^-: 989.3039. Found: 989.3069.

Synthesis of 8-(cyclohexylamino)-6-phenyl-5*H*-chromeno[4,3,2-*gh*]pyrrolo[3,4-*k*]phenanthridine-5,7(6*H*)-dione (20aq)

A solution of xanthone **8aq** (25 mg, 0.044 mmol) and iron (18 mg, 0.323 mmol) in acetic acid (1 mL) was heated at 130 °C under nitrogen until the starting xanthone was consumed (15 h). Then the organic phase was filtered over Celite, and washed with NaOH 2 M (3 × 20 mL), dried over Na_2SO_4 and purified by chromatographic column (gradient AcOEt : hexane) yielding the desired product **13aq** (12 mg, 54%), obtained as a red solid; mp: 190 °C; IR (cm^{-1}): 3423, 2924, 2849, 1745, 1693, 1586; ^1H NMR (500 MHz, $CDCl_3$) δ 9.82 (d, J = 8.4 Hz, 1H), 8.53 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.58–7.41 (m, 8H), 7.30 (t, J = 7.1 Hz, 1H), 7.15 (bs, NH, 1H), 7.08 (d, J = 8.0 Hz, 1H), 4.17 (m, 1H), 2.16 (m, 2H), 1.86 (m, 2H), 1.60–1.38 (m, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 168.9 (C), 166.8 (C), 152.3 (C), 145.9 (C), 144.9 (C), 144.7 (C), 134.6 (C), 132.4 (CH), 131.9 (C), 129.9 (CH), 129.4 (CH), 129.2 (CH), 128.9 (CH), 128.3 (CH), 127.1 (CH), 126.4 (CH), 125.6 (CH), 125.2 (CH), 124.3 (C), 122.3 (C), 121.0 (C), 119.0 (C), 118.4 (C), 117.8 (C), 116.6 (CH), 54.1 (CH), 35.1 (CH_2), 25.8 (CH_2), 24.9 (CH_2) ppm; MS (CI) m/z (%) 513 (M + 2, 33), 512 (M + 1, 59), 511 (M^+, 41), 478 (14), 350 (10); HRMS (EI) Calcd for $C_{33}H_{25}N_3O_3$: 511.1896. Found: 511.1892.

Conflicts of interest

There are no conflicts to declare.

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