Regioselective Synthesis of Dihydroxanthones and Xanthones through a Tandem Process

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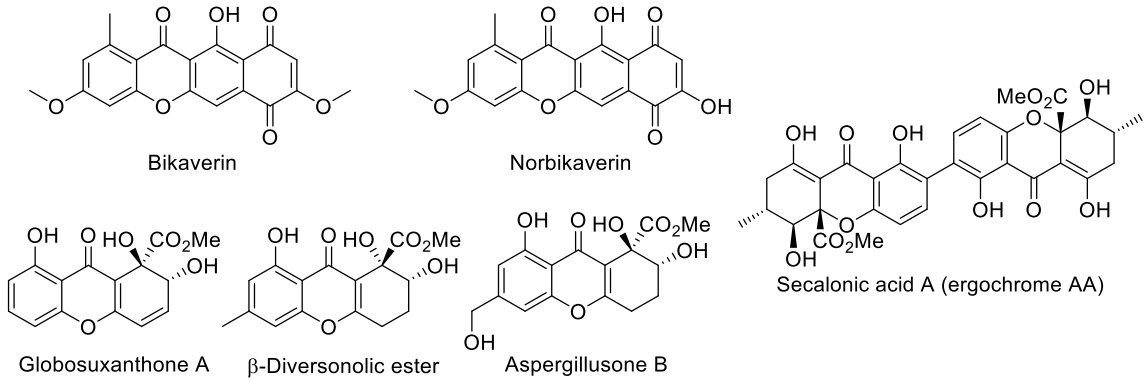
Introduction

Xanthones are important mycotoxin-related compounds present in many plants, fungi and lichens, which have demonstrated to be able to interact with different biological targets.[1] Importantly, hydroxyxanthones with different patterns of substitution have been reported to strongly inhibit MAO and diverse kinases, showing anti-tumoral and anti-inflammatory activity.[2] Furthermore, natural dihydroxanthones containing both hydroxyl and ester groups on position 1, such as monomeric globosuxanthones, diversonolic esters and aspergillusones,[3,4,5] and dimeric secalonic acids, ergoflavins, ergochrysins, and chrysergonic acid (Scheme 1),[6] have important antifungal, antibiotic, anticancer and anti-HIV activities.



Scheme 1. Different xanthones and dihydroxanthones present in nature

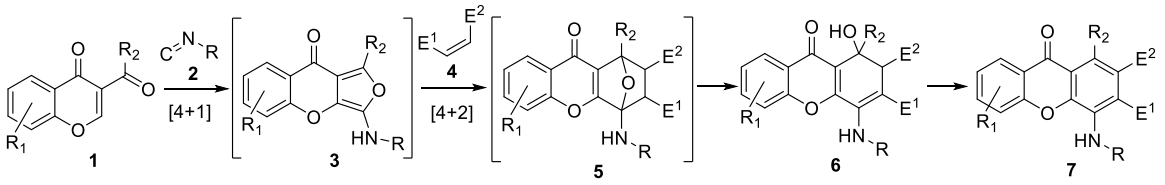
Although many non-natural xanthones containing diverse functional groups have been synthesized and their biological responses have been tested, the introduction of an amino substituent on the xanthone core has been scarcely explored. Amino groups are especially interesting, as they can be considered equivalent to hydroxyl groups, which are almost universally present in biologically active natural occurring xanthones.

The few known syntheses of aminoxanthones are typically based on the coupling of, either diaryleters or benzophenones, to build the xanthone tricyclic structure and the subsequent reduction of a nitro group to introduce the desired amino substituent. These synthetic procedures often involve harsh conditions and the use of strong acids, bases or transition metals. Environmentally unfriendly and long multistep processes and low overall yields usually make all these reactions noncompetitive. As an exception, a non-classical one-pot synthesis of aminoxanthones has been recently published by Hu and col. starting from 3-(1-Alkynyl)chromones and acetonitriles.[7] Consequently, the development of direct and efficient routes to structurally diverse xanthones is highly desirable.

Multicomponent reactions (MCR) are highly convergent processes characterized by the formation of several bonds in a single operation. We have recently reported a multicomponent reaction of anilines from α,β-unsaturated keto-esters, isocyanides and phthalimides.[9] The experimental simplicity and wide functional group tolerance of this new MCR make this type of process a very attractive alternative for the synthesis of xanthones.[8] Here we wish to report our results in the synthesis of both xanthones and dihydroxanthones with up to 4 diversification structural positions.

Results and Discussion

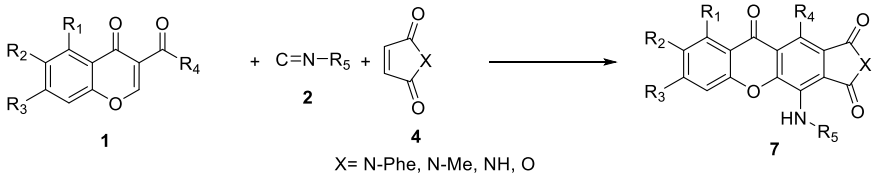
Starting from easily available 3-carbonylchromones,[10] isocyanides and different dienophiles we have teamed up to obtain the above mentioned products in a one pot tandem procedure through a [4+1]−[4+2] cycloaddition (Scheme 2).



Scheme 2

We hypothesize the mechanism would begin with the nucleophilic attack of isocyanide **2** to the electronically deficient carbon 2 of chromone **1** in a [4+1] cycloaddition, giving an iminolactone intermediate. This would tautomerize to aminofuran **3** that, in turn, would undergo a [4+2] cycloaddition reaction with the electrophile **4**. The 7-oxabicyclo[2.2.1]heptane **5** has not been isolated, as the assistance of the nitrogen lone pair would enable the *in situ* opening of the oxygen bridge and subsequent dehydration to directly afford the aromatic 4-aminoxanthone **7**. When the dienophile is a maleimide derivative, the dehydration process takes place at room temperature obtaining the expected 4-aminoxanthones with excellent yields up to 99% (Table 1). The scope of the reaction is wide, since different carbonyl chromones efectively lead to the desired products. The presence of electron withdrawing substituents on the carbonyl group considerably facilitate the reaction, but good results are also obtained if this is not the case, for example with formylchromones, although in these cases higher temperatures, up to 110ºC, were required. All the 4-aminoxanthones synthetized have a bright yellow or orange color and show an intense fluorescence that ranges from green to yellow or red.

Table 1. General synthesis of 4-aminoxanthones

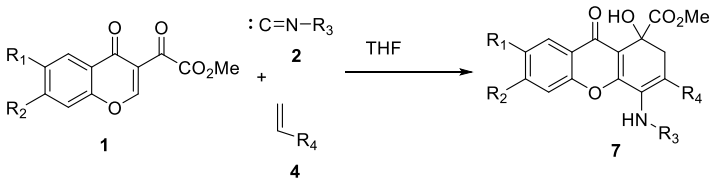


entry	R_1	R_2	R_3	R_4	X	R_5	T (ºC)	Time (h)	% yield
1	H	H	OMe	CO_2Me	N-C_6H_5	*c*C_6H_{11}	25	24	99[a]
2	H	Cl	H	CO_2Me	N-C_6H_5	*c*C_6H_{11}	35	96	81[a]
3	H	Me	H	CO_2Me	N-C_6H_5	*c*C_6H_{11}	25	24	75[a]
5	H	Cl	H	CO_2Me	N-C_6H_5	*t*Bu	35	120	85[a]
4	H	H	H	CO_2Me	N-CH_3	*c*C_6H_{11}	35	32	94[a]
5	H	H	OMe	CO_2Me	N-CH_3	*c*C_6H_{11}	35	23	81[a]
6	H	H	H	CO_2Me	O	*c*C_6H_{11}	25	96	83[a]
7	H	H	OMe	CO_2Me	O	*c*C_6H_{11}	25	72	87[a]
8	H	H	H	CO_2Me	NH	*c*C_6H_{11}	25	72	86[a]
9	H	H	OMe	CO_2Me	NH	$PhCH_2$	25	72	30[a]
10	H	H	H	*o*-NO_2Ph	N-C_6H_5	*c*C_6H_{11}	80	6,5	77[a]
11	H	H	H	*o*-NO_2Ph	O	*c*C_6H_{11}	80	22	88[a]
12	H	H	H	*p*-NO_2Ph	N-C_6H_5	*c*C_6H_{11}	80	35	93[a]
13	H	H	H	CF_3	N-C_6H_5	*c*C_6H_{11}	80	21	61[a]
14	H	H	OMe	CF_3	N-C_6H_5	*c*C_6H_{11}	80	13	58[a]
15	H	H	H	H	N-C_6H_5	*c*C_6H_{11}	110	41	89[b]
16	H	Me	H	H	NH	*c*C_6H_{11}	110	48	87[b]
17	H	Me	H	H	O	*c*C_6H_{11}	110	62	46[b]
18	H	Cl	H	H	N-C_6H_5	*c*C_6H_{11}	110	25	92[b]
19	H	H	H	H	N-C_6H_5	CH_2CO_2*t*Bu	110	95	85[b]
20	H	H	H	H	N-C_6H_5	*t*Bu	110	123	58[b]

[a]General procedure: 1.1 equiv. of isocyanide and 1.1 equiv. of dienophile was added under nitrogen to a 1 equiv. solution of chromone in THF.b Reaction was carried out at toluene reflux.

Thus, the proposed mechanism suggests the dehydration of hydroxyxanthone intermediate **6** is possible due to the acidity of the hydrogen on position 2, which enables immediate formation of aromatic 4-aminoxanthone **7** (Scheme 2). We reason that elimination of water would be much more difficult in the absence of an electron-withdrawing group on position 2, and in that case it could be possible to isolate the intermediate 1-hydroxy-1*H*-xanthen-9(2*H*)-one (**6**). With this in mind, we have used asymmetric dienophiles containing only one electron-withdrawing group, such as acrylonitrile and methy vinyl ketone. They regioselectively afforded 1-hydroxy-1*H*-xanthen-9(2*H*)-ones with the substituent on position C3, which were unable to dehydrate in the reaction conditions (Table 2).

Table 2. General synthesis of 1-hydroxy-1*H*-xanthen-9(2*H*)-ones

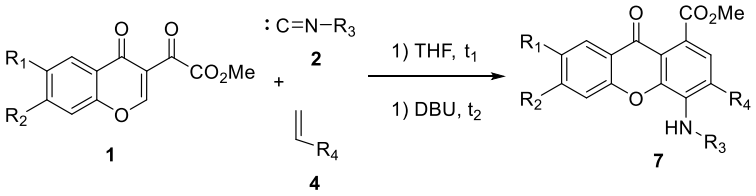


entry	R_1	R_2	R_3	R_4	Time (h)	% yield
1	Me	H	*c*C_6H_{11}	CN	2	76[a]
2	H	H	*c*C_6H_{11}	CN	2	81[a]
3	H	OMe	*c*C_6H_{11}	CN	4.5	82[a]
4	Cl	H	*c*C_6H_{11}	CN	2	83[a]
5	H	H	*p*MeOPh	CN	9	28[a]
6	Me	H	*c*C_6H_{11}	COMe	1	78[b]
7	H	OMe	*c*C_6H_{11}	COMe	0.5	74[b]
8	Cl	H	*c*C_6H_{11}	COMe	1	90[b]
9	H	H	*c*C_6H_{11}	COMe	0.5	70[b]
10	Me	H	*p*MeOPh	COMe	2	62[b]
11	Me	H	C_5H_{11}	COMe	1	83[b]

[a]Method A: A solution of **1** (1 equiv), **2** (1.2 equiv), and **4** (2 equiv) in THF is heated 2-9 h at 70 ºC. [b]Method B: A solution of **1** (1 equiv), **2** (1.2 equiv), and **4** (1.2 equiv) in THF is irradiated with MW 0.5-2 h in a close vial at 100 ºC.

This synthesis efficiently affords a variety of dihydroxanthones structurally similar to bioactive ergochromes.[11] The yields are from moderate to good and the obtained hydroxydihydroxanthenones **6** could be readily aromatized by microwave irradiation at 140 °C in the presence of DBU to give the corresponding aromatic xanthones (results not shown). These reactions were also carried out in a one-pot sequential procedure, with no isolation of the dihydroxanthone intermediate. In all cases the reaction was completely regioselective affording the product with the electron-withdrawing group from the dienophile in position 3 of the xanthone (Table 3).

Table 3. General synthesis of 1-hydroxy-1*H*-xanthen-9(2*H*)-ones



entry	R_1	R_2	R_3	R_4	t_1/t_2 (h)	% yield
1	Me	H	*c*C_6H_{11}	CN	5/1.5	68[a]
2	H	H	*c*C_6H_{11}	CN	2/0.5	78[a]
3	H	H	*c*C_6H_{11}	CN	0.5/0.2	75[b]
4	H	OMe	*c*C_6H_{11}	CN	9/1	65[a]
5	Cl	H	*c*C_6H_{11}	CN	2.5/0.5	70[a]
6	Me	H	*c*C_6H_{11}	COMe	6.5/1	70[b]
7	H	OMe	*c*C_6H_{11}	COMe	1/1.5	75[b]
8	Cl	H	*c*C_6H_{11}	COMe	1/0.3	68[b]
9	H	H	*c*C_6H_{11}	COMe	0.5/1	76[b]
10	Me	H	*p*MeOPh	COMe	3/0.5	70[b]
11	Me	H	C_5H_{11}	COMe	1.5/1	44[b]
12	H	OMe	*t*-Bu	CN	3/0.5	69[a]
13	H	OMe	*t*-Bu	CN	1/0.2	69[b]
14	Cl	H	*t*-Bu	CN	3.5/0.5	78[a]
15	Cl	H	C_5H_{11}	COMe	0.5/0.5	48[b]

[a]Method A: A solution of **1** (1 equiv), **2** (1.2 equiv), and **4** (2 equiv) in THF is heated 2-9 h at 70 ºC, then 2 equiv DBU is added, and the reaction mixture is heated further 25-75 min at the same temperature. [b]Method B: A solution of **1** (1 equiv), **2** (1.2 equiv), and **4** (1.2 equiv) in THF is irradiated with MW 0.5-6h, then 2 equiv DBU is added, and the reaction mixture is further irradiated 10-90 min.

Conclusion

We have developed a novel, straightforward, tandem synthesis polysubstituted 4-aminoxanthones starting from 3-carbonylchromones, isocyanides and dienophiles. The products are available in few hours and, in many cases, precipitate from the reaction medium, no requiring any further purification. The proposed mechanism has been confirmed by the isolation of the intermediate hydroxydihydroxanthenones, which are *per se* an interesting biological synthetic scaffold. This constitutes the first example of a multicomponent reaction to obtain xanthones and hydroxyxanthones, where three new carbon-carbon bonds are formed.

Acknowledgements

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