An efficient copper-catalytic system for performing intramolecular *O*-arylation reactions in aqueous media. New synthesis of xanthones†‡

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Received 15th January 2009, Accepted 6th March 2009
First published as an Advance Article on the web 19th March 2009
DOI: 10.1039/b900931k

A safe, efficient protocol for the copper-catalysed intramolecular *O*-arylation of 2-halobenzophenones on water to afford the valuable xanthone framework is reported. The recovery and the successful reutilization of the aqueous solution containing the copper catalyst are also presented. Moreover, the scalability and the easy setup and purification tasks of this sustainable method make it appealing for bulk industry applications.

Introduction

The xanthone skeleton constitutes the core of an important natural and biologically active family of compounds present in higher plants and microorganisms. These secondary metabolites have interesting pharmaceutical properties such as anticancer,[1] antithrombotic,[2] antihypertensive,[2] antibacterial,[3] antitumoral,[4] opiaceous,[5] cytotoxic,[6] antiviral[7] and anti-inflammatory activity,[7] among others. Moreover, they are also effective against pathogenic fungi[8] and in the inhibition of both gastric secretion[9] and biosynthesis of prostaglandin E2.[10] According to several authors, the biological role of xanthones can be modulated by introducing specific substituents in their structure (Fig. 1).[11,12]

Typically employed methods for the synthesis of the xanthone scaffold imply the previous formation of benzophenones or diarylethers by means of harsh experimental conditions or harmful reactants.[15,16] In recent years, alternative routes to access this appealing family of compounds have been developed. Some of them involve photooxidative cyclisation[17] or cycloaddition[18] of 2-styrylchromones. More recently, another synthesis of the xanthone core was carried out *via* the Diels–Alder reaction of chromone-3-carboxaldehydes with *o*-benzoquinodimethane, followed by the *in situ* oxidation of the cycloadducts.[19] Furthermore, Larock and co-workers[20] have designed a novel strategy to prepare xanthones starting from salicylates and commercially available silylaryl triflates, which act as aryne precursors in the presence of four equivalents of CsF. Under these mild reaction conditions an annulation step takes place to afford the target products in a one-pot synthesis. They have also prepared xanthones by palladium-catalysed arene C–H addition to nitriles

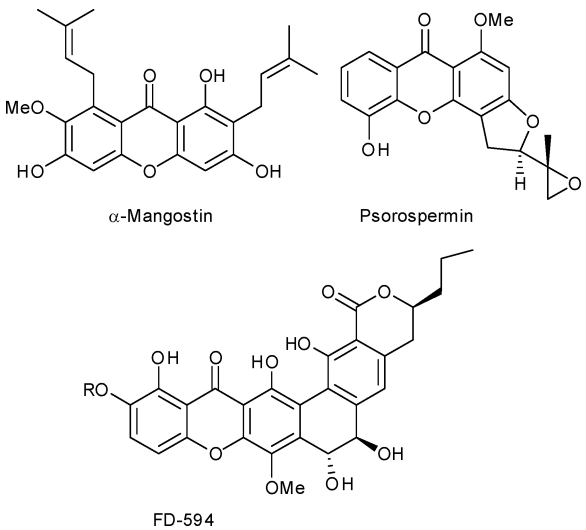

Fig. 1 Some relevant natural xanthones,[13] and the antibiotic FD-594.[14]

through the formation of ketones from substituted phenols and 2-fluorobenzonitriles, followed by an intramolecular cyclisation in the presence of K_2CO_3.[21] Another approach to the xanthone framework accomplished by the same group implied an aryl to imidoyl palladium migration process involving intramolecular C–H activation.[22]

Although the latter methods are elegant and efficient for the synthesis of the xanthone core, the drawbacks of palladium catalytic systems, such as the high cost of the metal, its relative toxicity, its air/moisture sensitivity and the difficulties found on its removal at purification steps, have limited their use in bulk industry.

An emerging alternative to most palladium-catalysed cross-coupling processes is the use of copper in this context.[23,24] Indeed, the copper-catalysed Ullmann-type coupling of phenols with aryl halides has been steadily studied.[25–28] These classical Ullmann conditions were strongly limited by the large amounts of copper catalysts and the high reaction temperatures required (~200 °C), the poor substrate scope and the low to moderate yields reached.[29] As a representative example, Watson reported the synthesis of a pyrroloxanthone by a sequence of Ullmann

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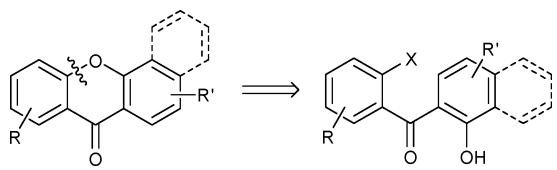
† Dedicated to Professor Luis Castedo on the occasion of his 70th birthday.

‡ Electronic supplementary information (ESI) available: Typical experimental procedures, including spectroscopic and analytical data for all the new intermediates along with NMR spectra of the new compounds. See DOI: 10.1039/b900931k

coupling/F–C acylation.[29] Stoichiometric amounts of copper (Cu bronze and CuI), anhydrous conditions and temperatures around 200 °C were required for the Ullmann coupling step. All the aforementioned factors made these strategies unappealing for the industry and difficult to scale-up. Research on the use of bidentate ligands, such as aliphatic diamines,[30] 1,10-phenantroline,[31] ethylene glycol,[32] β-keto esters[33] and PPAPM,[34] and additives (8-hydroxyquinoline,[35] 1-naphthoic acid,[25] amino acids,[36] Schiff bases,[37] *inter alia*) has attracted much attention, since they overcome some of these inconvenient drawbacks. Moreover, the use of soluble copper-complexes,[38] ligand free conditions,[39] Cu nanoparticles[40] or microwave[41,42] and ultrasonic[43] irradiation has also contributed positively to the efficient development of copper-catalysed *O*-arylation of substituted phenols.[44] Therefore, these modifications not only shorten the reaction time but also allow the performance of the reactions under milder conditions.

The pursuit of inexpensive and more benign and environmentally friendly methodologies for the synthesis of xanthones still remains a challenge. In this context, and considering the experience of our group in the preparation of heterocycles through copper-assisted arylation processes in aqueous media,[45] we envisaged an approach based on the latter strategy to access a new family of xanthones (Scheme 1). The advantages derived from the use of water as solvent are numerous, such as safety, non-toxicity, low cost, easy-handling, availability and greater chemoselectivity, compared with organic solvents.[46,47]



Scheme 1 Retrosynthetic pathway to access the xanthone framework.

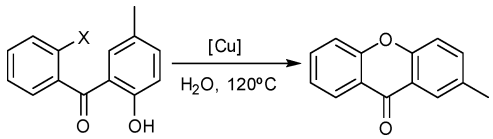
Herein, we report an active catalytic system for the straightforward synthesis of the xanthone scaffold from *o*-halobenzophenones through a copper-catalysed intramolecular *O*-arylation reaction in water as the only solvent. Taking into account the easy setup, recyclability and the sustainability of this procedure, it could be transferred to industrial purposes.

Results and discussion

Initially, in order to optimise the copper-catalysed *O*-arylation reaction to furnish target xanthone **1a**, 2-bromo- and 2-iodobenzophenones **2a** and **2a′** were selected as model substrates (Table 1). These key intermediates were easily prepared in a one-step Friedel–Crafts acylation with graphite and methanesulfonic acid in relatively short times (3–4 hours), following the procedure described in the literature.[48] The main reason to choose this modern protocol was the recyclability of the employed cheap graphite, which would make our whole synthetic sequence even more environmentally friendly.

Accordingly, a range of assays employing a survey of copper sources and commercially available ligands in an aqueous solution were performed. The main results of the optimisation

Table 1 Selected *O*-arylation assays for the synthesis of xanthone **1a**



2a X = I
2a' X = Br
1a

Entry	X	Copper salt, base, ligand[a,b]	Yield (%)[c]
1	I	CuI, TMEDA	83
2	Br	CuI, TMEDA	90
3	I	CuI, CHDA	69
4[d]	I	CuI, NMP, K_2CO_3	95
5[d,e]	Br	CuI, NMP, K_2CO_3	59
6[d]	Br	CuI, NDMP, K_2CO_3	75
7[d]	I	CuI, D, L-proline, K_2CO_3	66
8	I	CuI, PMDTA	57
9[d]	I	CuI, BPDA, K_2CO_3	32
10[d,f,g]	I	CuI, dba, K_3PO_4	tr
11	Br	CuI, TMEDA, K_2CO_3	79
12[g]	Cl	CuI, TMEDA	tr
13	Br	$Cu(OTf)_2$, TMEDA	62
14	Br	$Cu(OAc)_2 \cdot H_2O$, TMEDA	89
15	Br	CuBr, TMEDA	86
16	Br	Cu_2O, TMEDA	64
17	Br	TMEDA	10
18	Br	CuI	—
19	Br	—	—

[a] 10 mol% of the Cu salt and 3.5 equiv. of ligand when no additional base was used. All reactions were run in water (12 mL per mmol of **2**) at 120 °C. [b] CHDA: *trans*-1,2-diaminocyclohexane; NDMP: *N*,*N*′-dimethylpiperazine; dba: *trans*,*trans*-dibenzylidene acetone; PMDTA: *N*,*N*,*N*′,*N*′,*N*′-pentamethyldiethylenetriamine; NMP: *N*-methylpiperazine; TMEDA: *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; BPDA: *rac*-2,2′-biphenyldiamine. [c] Yield of isolated products. [d] 20 mol% of ligand and 2.0 equiv. of base. [e] A similar yield was obtained when Cs_2CO_3 was used. [f] Complex mixture of inseparable products. [g] Only traces of the cyclised product were detected.

process are displayed in Table 1. Interestingly, when different copper salts were employed (Table 1, entries 2, 13–16), the yields obtained were quite similar. The possibility of using different copper sources, regardless of their oxidation state, to perform the target cyclisation makes this methodology advantageous and attractive from a synthetic point of view.

Although CuI, $Cu(OAc)_2 \cdot H_2O$ and CuBr delivered the xanthone **1a** in fairly similar yields (86–90% yield), copper (I) iodide was selected due to its air and moisture stability. Then, we evaluated the combination of CuI with several commercially available aliphatic diamines, such as TMEDA, CHDA or PMDTA. As shown in Table 1, the more basic TMEDA provided considerably better yields (entry 1 *vs.* 3 and 8). Combining catalytic amounts of CuI along with other nitrogen containing ligands (NMP, NDMP, D,L-proline and BPDA) and additional bases gave in most cases poorer yields (entries 4–7 and 9). The combination of CuI and NMP in catalytic amounts with K_2CO_3 as base seemed to be a good choice, as it provided an excellent yield in the case of 2-iodobenzophenone **2a**. However, a considerably lower yield was obtained starting from the 2-bromo analogue **2a′** (entries 4–5).[49] An attempt to use the cheap dba as ligand for this intramolecular *O*-arylation reaction gave a complex mixture of inseparable products (entry 10). Unfortunately, the

2-chlorobenzophenone derivative afforded negligible results and the product was hardly detected (entry 12).

Finally, we decided to run three blank experiments. The first one (Table 1, entry 17) was to verify that the copper was really necessary for the intramolecular *O*-arylation process, and to discard a classical aromatic substitution (S_NAr) in which the transition metal should not play any role. We recovered the unreacted starting material as the main product, just isolating a small amount (10%) of target xanthone **1a**, thus confirming the requirement of a copper complex to promote an effective *O*-arylation (Table 1, entry 2 *vs.* 17). The second assay (entry 18) proved that TMEDA (which probably acts both as base and ligand)[45] was clearly needed for the reaction, since otherwise no product was detected. Finally, no reaction was observed when we stirred 2-bromobenzophenone **2a′** in neat water (entry 19).

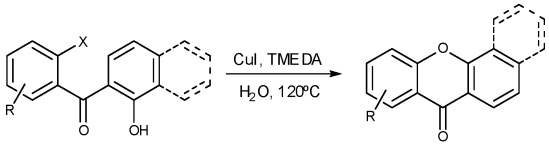
Taking into account all the experimental results it was decided that the best conditions involved stirring the starting material in the presence of 10 mol% of CuI and 3.5 equiv. of TMEDA in water at 120 °C. The ease of the reaction setup, the absence of side products and the lack of requirement for an inert atmosphere should be highlighted.

The Ullmann-type coupling process of substituted phenols with aryl halides has traditionally been accomplished using toxic and high-boiling organic solvents as reaction media.[25–28] A comparison of our procedure with the typically employed strategies to perform this kind of *O*-arylation reaction revealed that the target xanthone **1a** is obtained in much better yields when employing our simple protocol. When we carried out the reaction using the procedure reported by Buchwald and co-workers[25] in 1997 (which involved the use of catalytic amounts of unstable $(CuOTf)_2{\cdot}C_6H_6$ and EtOAc in the presence of Cs_2CO_3 and 1-naphthoic acid as additive in boiling toluene) and the method developed by Chang *et al.*[26] (catalytic amounts of CuI along with ^{n}BuNBr as phase transfer catalyst and K_3PO_4 in DMF at reflux) we only achieved yields of 45 and 63%, respectively. These two parallel experiments outlined the efficiency of our "on water" strategy.

Encouraged by these remarkable results, we decided to evaluate the scope and limitations of this strategy. Accordingly, the preparation of several differently substituted 2-iodo- and 2-bromobenzophenones **2** was carried out from commercially available 2-halobenzoic acids and substituted phenols by means of the aforementioned Friedel–Crafts acylation.[48] These precursors were subjected to the above described optimal conditions to undergo the intramolecular *O*-arylation reaction affording the cyclisation products with the results shown in Table 2.

Surprisingly, both 2-iodo- and 2-bromobenzophenones **2** delivered the cyclisation products with excellent results, regardless of the nature of the halogen substituent (83 *vs.* 90% and 84 *vs.* 73%, in entries 1 and 2, respectively). Only when the hydroxyarene moiety was 1-hydroxynaphthalene, was a remarkable difference in the yields found (62% from **2d** and 89% from **2d′**, Table 2, entry 4). In this case, the conversion of the reaction when **2d** was employed as substrate was incomplete, finding significant amounts of the unreacted starting material. Following with the hydroxyl group containing moiety, a relatively lower yield was obtained when electron-enriched derivative **2c** was employed (entry 3). With regard to the *o*-halide containing moiety, substrates bearing additional halogens such as fluoro or chloro

Table 2 Preparation of differently substituted xanthones **1**[a]



2 X=I, Br **1**

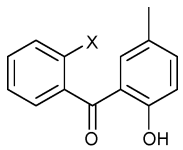
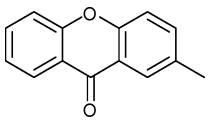
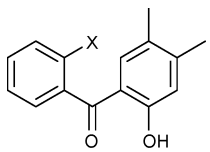
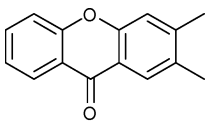
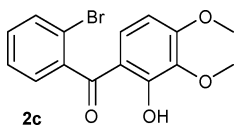
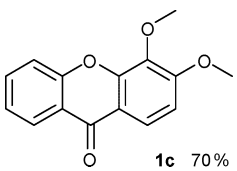
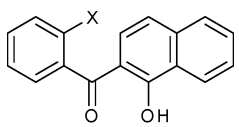
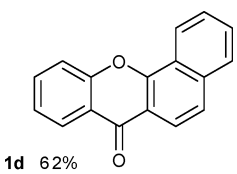
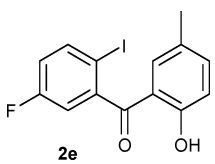
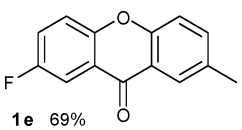
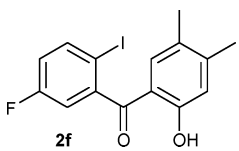
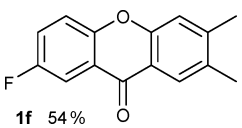
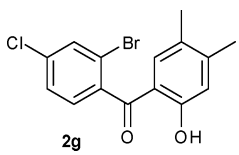
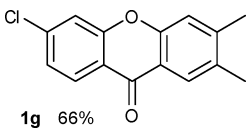
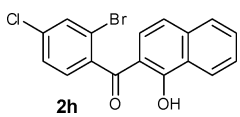
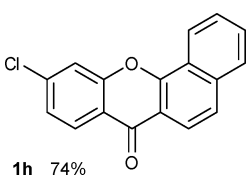
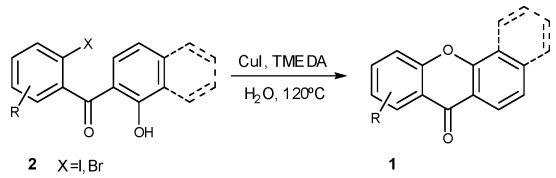
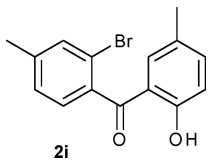
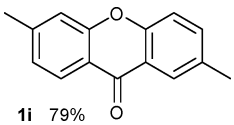
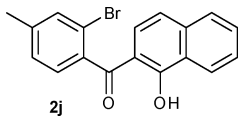
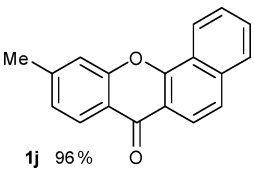
Entry	Substrate **2**	Xanthone **1**[b]
1	 **2a** X = I **2a'** X = Br	 **1a** 83%, 95%[c] 90%
2	 **2b** X = I **2b'** X = Br	 **1b** 84% 73%
3	 **2c**	 **1c** 70%
4	 **2d** X = I **2d'** X = Br	 **1d** 62% 89%
5	 **2e**	 **1e** 69%
6	 **2f**	 **1f** 54%
7	 **2g**	 **1g** 66%
8	 **2h**	 **1h** 74%

Table 2 *(Contd.)*



2 X=I, Br 1

Entry	Substrate **2**	Xanthone **1**[b]
9	 **2i**	 **1i** 79%
10	 **2j**	 **1j** 96%

[a] 10 mol% of CuI, 3.5 equiv. of TMEDA and H_2O (12 mL per mmol of **2**) at 120 °C. [b] Yield of isolated products. [c] 10 mol% of CuI, 20 mol% of NMP, 2 equiv. of K_2CO_3 and H_2O (12 mL per mmol of **2a**) at 120 °C.

groups provided slightly lower yields (Table 2, entries 5–8). The presence of these halogens offer the possibility of carrying out a second aromatic substitution process or metal catalysed cross-couplings (Suzuki, Heck, *etc.*) to achieve a more substituted xanthone. In general, it could be affirmed that there is no clear trend related to the electronic nature of the substituents.

At this stage, we decided to evaluate the reutilization of the aqueous solution we used to prepare the xanthone **1a** starting from 2-bromobenzophenone **2a′**. This green solution presumably contained a water soluble copper-TMEDA complex formed during the process. Remarkably, when we reused this aqueous solution the target xanthone **1a** was obtained with an excellent yield of 97%, slightly better than the one obtained in the first run (90%). It should be pointed out that an additional extra amount of TMEDA had to be added to the reaction, due to its supposed double role in the process.[45] After the second run, a clear change of colour of the aqueous solution was observed, from green to brown. The third run with this brown water solution delivered the cyclised product **1a** in a still good yield of 58%, but observing in this case some unreacted starting material.

Finally, the scale-up of our method to 1 and 48 grams starting from the 2-bromobenzophenone **2a′** resulted in excellent results, obtaining xanthone **1a** in 93% and 91% yields, respectively, a bit higher ones than at small scale. This preliminary result opens the possibility of a multigram entry to biologically relevant xanthones.

Conclusions

In summary, a highly practical and sustainable methodology for the synthesis of the very valuable xanthone framework through a copper-catalysed intramolecular *O*-arylation process is presented. Considering that the appealing xanthone scaffold has normally been prepared by using harmful reagents and solvents, the reported protocol delivers the target tricyclic skeleton in good to excellent yields exclusively in a safe, harmless aqueous medium. The recyclability, scalability and the easy reaction setup combined with the low cost of the starting materials make this simple method transferable to pharmaceutical purposes. Finally, it can be outlined that several commercially available copper salts afforded the cyclisation products in fairly similar yields, not limiting the procedure to the use of only one copper source.

Experimental

Typical procedure

2-Methylxanthen-9-one (1a). [22] A screw-capped tube (approximate volume: 18 mL) was charged with 2-iodoarylbenzophenone **2a** (108.1 mg, 0.32 mmol), CuI (6.1 mg, 0.032 mmol), TMEDA (0.17 mL, 1.12 mmol) and water (3.8 mL) at room temperature. After closing, the tube was heated to 120 °C for 15 h, allowed to cool to room temperature and the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a solid residue, which was redissolved and filtered through a short pad of silica gel. The filtrate was evaporated under reduced pressure to provide the target xanthone **1a** (55.9 mg, 83%) as a white powder.

The typical procedure was followed starting from 2-bromoarylbenzophenone **2a′** (92.2 mg, 0.31 mmol) and CuI (6.2 mg, 0.032 mmol) to afford xanthone **1a** (60.1 mg, 90%) as a white powder. In a scale-up experiment, the typical procedure (a round-bottom flask closed with a stopper was employed) was applied to 2-bromoarylbenzophenone **2a′** (48.0 g, 0.16 mol) and CuI (3.1 g, 0.016 mol) to provide xanthone **1a** (30.61 g, 91%) as a white powder.

2,3-Dimethylxanthen-9-one (1b). [20] The typical procedure was followed starting from 2-iodoarylbenzophenone **2b** (88.2 mg, 0.25 mmol) and CuI (4.8 mg, 0.025 mmol) to afford xanthone **1b** (47.1 mg, 84%) as a white powder.

The typical procedure was followed starting from 2-bromoarylbenzophenone **2b′** (84.5 mg, 0.28 mmol) and CuI (5.3 mg, 0.028 mmol). After a short flash chromatography (20 mol% EtOAc/hexane) xanthone **1b** (42.3 mg, 73%) was obtained as a white powder.

3,4-Dimethoxyxanthen-9-one (1c). The typical procedure was followed starting from 2-bromoarylbenzophenone **2c** (99.9 mg, 0.30 mmol) and CuI (5.7 mg, 0.030 mmol). After a short flash chromatography (20 mol% EtOAc/hexane) xanthone **1c** (53.7 mg, 70%) was obtained as a white powder. Mp 150–152 °C (from hexane); IR ν_{max}(KBr)/cm^{-1} 1661, 1602, 1455, 1290 and 1091; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 4.01 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 7.01 (1H, d, *J* 9.0 Hz, H_2), 7.34–7.39 (1H, m, H_{arom}), 7.55–7.57 (1H, m, H_{arom}), 7.68–7.74 (1H, m, H_{arom}), 8.09 (1H, d, *J* 9.0 Hz, H_1) and 8.32 (1H, dd, *J* 7.9 and 1.7 Hz, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 56.4, 61.5 (OCH_3), 108.6 (C_2), 116.7 (C_{9a}), 118.0 (C_5),

121.5 (C_{8a}), 122.4, 123.9, 126.6 (C_{arom}-H), 134.5 (C_6), 136.4 (C_4), 150.6 (C_{4a}), 156.1 (C_{4b}, C_3), 157.5 (C_3, C_{4b}) and 176.5 (CO); MS (CI) *m/z* 258 (M + 2, 13%), 257 (M + 1, 100) and 256 (M^+, 37). HRMS (CI) [M + 1]: calculated for $C_{15}H_{13}O_4$, 257.0814; found, 257.0813.

7*H*-Benzo[*c*]xanthen-7-one (1d). [20] The typical procedure was followed starting from 2-iodoarylbenzophenone **2d** (122.8 mg, 0.32 mmol) and CuI (6.2 mg, 0.033 mmol). After a short flash chromatography (20 mol% EtOAc/hexane) xanthone **1d** (46.0 mg, 62%) was obtained as a white powder.

The typical procedure was followed starting from 2-bromoarylbenzophenone **2d′** (93.0 mg, 0.28 mmol) and CuI (5.4 mg, 0.028 mmol) to afford xanthone **1d** (63.1 mg, 89%) as a white powder.

2-Fluoro-7-methylxanthen-9-one (1e). The typical procedure was followed starting from 2-iodoarylbenzophenone **2e** (66.5 mg, 0.18 mmol) and CuI (3.5 mg, 0.018 mmol). After a short flash chromatography (20 mol% EtOAc/hexane) xanthone **1e** (28.2 mg, 69%) was obtained as a white powder. Mp 152–154 °C (from hexane); IR ν_{max}(KBr)/cm^{-1} 1661 and 1473; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 2.46 (3H, s, CH_3), 7.37 (1H, d, *J* 8.5 Hz, H_5), 7.41–7.49 (2H, m, H_8), 7.52–7.55 (1H, m, H_{arom}), 7.95 (1H, dd, *J* 8.3 and 2.9 Hz, H_6) and 8.07–8.08 (1H, m, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 20.8 (CH_3), 111.1 (d, *J* 25.4 Hz, C_1), 117.7 (C_5), 119.9 (d, *J* 7.9 Hz, C_4), 120.6 (C_{8a}), 122.6 (C_{9a}), 122.7 (d, *J* 25.3 Hz, C_3), 125.9 (C_8), 133.9 (C_7), 136.6 (C_6), 152.3 (d, *J* 1.4 Hz, C_{4a}), 154.3 (C_{4b}), 158.6 (d, *J* 244.8 Hz, C_2) and 176.6 (d, *J* 2.2 Hz, CO); MS (CI) *m/z*: 229 (M + 1, 100%), 228 (M^+, 41) and 209 (12). HRMS (CI) [M + 1]: calculated for $C_{14}H_{10}FO_2$, 229.0665; found, 229.0659.

2-Fluoro-6,7-dimethylxanthen-9-one (1f). The typical procedure was followed starting from 2-iodoarylbenzophenone **2f** (106.9 mg, 0.29 mmol) and CuI (5.2 mg, 0.027 mmol). After a short flash chromatography (10 mol% EtOAc/hexane) xanthone **1f** (35.0 mg, 54%) was obtained as a white powder. Mp 168–169 °C (from hexane); IR ν_{max}(KBr)/cm^{-1} 1661, 1625, 1467 and 1279; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 2.37 (3H, s, CH_3), 2.39 (3H, s, CH_3), 7.25–7.26 (1H, m, H_{arom}), 7.33–7.39 (2H, m, H_{arom}), 7.66–7.68 (1H, m, H_{arom}) and 7.72 (1H, s, H_8); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 19.2 (s, CH_3), 20.6 (s, CH_3), 111.3 (d, *J* 25.2 Hz, C_1), 118.0 (C_5), 118.8 (C_{8a}), 119.8 (d, *J* 7.8 Hz, C_4), 122.4 (d, *J* 25.3 Hz, C_3), 122.7 (d, *J* 7.1 Hz, C_{9a}), 126.2 (C_8), 133.3 (C_7), 145.8 (C_6), 152.3 (d, *J* 1.4 Hz, C_{4a}), 154.6 (C_{4b}), 158.5 (d, *J* 244.6 Hz, C_2) and 176.3 (d, *J* 2.1 Hz, CO); MS (CI) *m/z*: 243 (M + 1, 100%) and 242 (M^+, 45), 223 (15). HRMS (CI) [M + 1]: calculated for $C_{15}H_{12}FO_2$, 243.0821; found, 243.0816.

3-Chloro-6,7-dimethylxanthen-9-one (1g). The typical procedure was followed starting from 2-iodoarylbenzophenone **2g** (99.3 mg, 0.29 mmol) and CuI (5.6 mg, 0.029 mmol). After a short flash chromatography (20 mol% EtOAc, hexane) xanthone **1g** (50.1 mg, 66%) was obtained as a white powder. Mp 173–174 °C (from hexane); IR ν_{max}(KBr)/cm^{-1} 1655, 1596 and 1420; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 2.35 (3H, s, CH_3), 2.38 (3H, s, CH_3), 7.21 (s, 1H, H_5), 7.30 (dd, *J* 8.5, 1.8 Hz, 1H, H_2), 7.44 (1H, d, *J* 1.8 Hz, H_4), 8.00 (1H, s, H_8) and 8.23 (1H, d, *J* 8.5 Hz, H_1); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 19.1 (CH_3), 20.5 (CH_3), 117.9 (C_4, C_5), 118.0 (C_5, C_4), 119.5 (C_{8a}, C_{8b}), 120.4 (C_{8b}, C_{8a}), 124.4, 126.2, 128.0 (C_{arom}-H), 133.5, 140.3, 145.7 (C_{arom}-C), 154.5 (C_{4b}), 156.2 (C_{4a}) and 176.1 (CO); MS (CI) *m/z*: 259 (M + 1, 100%) and 258 (M^+, 42). HRMS (CI) [M + 1]: calculated for $C_{15}H_{12}ClO_2$, 259.0526; found, 259.0526.

10-Chloro-7*H*-benzo[*c*]xanthen-7-one (1h). The typical procedure was followed starting from 2-bromoarylbenzophenone **2h** (91.9 mg, 0.25 mmol) and CuI (4.8 mg, 0.025 mmol). After a short flash chromatography (20 mol% EtOAc/hexane) xanthone **1h** (53.0 mg, 74%) was obtained as a white powder. Mp 204–205 °C (from hexane); IR ν_{max}(KBr)/cm^{-1} 1655, 1602, 1431, 1379 and 1085; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 7.38 (1H, dd, *J* 8.5 and 1.9 Hz, H_{arom}), 7.64–7.63 (4H, m, H_{arom}), 7.88–7.91 (1H, m, H_{arom}), 8.20 (1H, d, *J* 8.2 Hz, H_{arom}), 8.29 (1H, d, *J* 8.5 Hz, H_{arom}) and 8.54–8.57 (1H, m, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 117.5 (C_{6a}), 118.0 (C_{11}), 120.8 (C_{7a}), 121.2, 122.6 (C_{arom}-H), 123.7 (C_{11c}), 124.4, 125.2, 127.0, 127.9, 128.1, 129.7 (C_{arom}-H), 136.5 (C_{4a}), 140.3 (C_{10}), 153.4 (C_{11b}), 155.7 (C_{11a}) and 175.9 (CO); MS (CI) *m/z*: 283 (M + 3, 34%), 282 (M + 2, 31), 281 (M + 1, 100), 280 (M^+, 43) and 245 (10). HRMS (CI) [M + 1]: calculated for $C_{17}H_{10}ClO_2$, 281.0369; found, 281.0367.

2,6-Dimethylxanthen-9-one (1i). The typical procedure was followed starting from 2-bromoarylbenzophenone **2i** (98.3 mg, 0.32 mmol) and CuI (6.1 mg, 0.032 mmol) to afford xanthone **1i** (57.1 mg, 79%) as a white powder. Mp 118–119 °C (from hexane); IR ν_{max}(KBr)/cm^{-1} 1655, 1619, 1437, 1302 and 1226; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 2.45 (3H, s, CH_3), 2.48 (3H, s, CH_3), 7.14–7.17 (1H, m, H_{arom}), 7.24–7.25 (1H, m, H_{arom}), 7.35 (1H, d, *J* 8.5 Hz, H_4), 7.50 (1H, dd, *J* 8.5 and 2.2 Hz, H_3), 8.09–8.10 (1H, m, H_{arom}) and 8.20 (1H, d, *J* 8.1 Hz, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 20.8 (CH_3), 21.9 (CH_3), 117.6 (C_5), 119.5 (C_{8a}), 121.5 (C_{9a}), 125.2, 125.9, 126.5 (C_{arom}-H), 133.5 (C_2), 135.8 (C_3), 146.1 (C_6), 154.3 (C_{4a}), 156.3 (C_{4b}) and 177.0 (CO); MS (CI) *m/z*: 225 (M + 1, 100%) and 224 (M^+, 4%). HRMS (CI) [M + 1]: calculated for $C_{15}H_{13}O_2$, 225.0916; found, 225.0907.

10-Methyl-7*H*-benzo[*c*]xanthen-7-one (1j). The typical procedure was followed starting from 2-bromoarylbenzophenone **2j** (91.6 mg, 0.27 mmol) and CuI (5.1 mg, 0.026 mmol) to afford xanthone **1j** (67.1 mg, 96%) as a white powder. Mp 220 °C (decomposition); IR ν_{max}(KBr)/cm^{-1} 1643, 1437, 1379 and 1085; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 2.51 (3H, s, CH_3), 7.19–7.20 (1H, m, H_{arom}), 7.13–7.14 (1H, m, H_{arom}), 7.61–7.69 (3H, m, H_{arom}), 7.86–7.89 (1H, m, H_{arom}), 8.22–8.25 (2H, m, H_{arom}) and 8.56–8.59 (1H, m, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 117.5 (C_{6a}, C_{7a}), 117.7 (C_{arom}-H), 120.1 (C_{7a}, C_{6a}), 121.5, 122.7, 123.7 (C_{arom}-H), 124.0 (C_{11c}), 125.8, 126.2, 126.7, 128.0, 129.3 (C_{arom}-H), 136.4 (C_{4a}), 145.7 (C_9), 153.4 (C_{11b}), 155.7 (C_{11a}) and 176.6 (CO); MS (CI) *m/z*: 262 (M + 2, 19%), 261 (M + 1, 100) and 260 (M^+, 40). HRMS (CI) [M + 1]: calculated for $C_{18}H_{13}O_2$, 261.0916; found, 261.0918.

Acknowledgements

This research was supported by the University of the Basque Country/Regional Government of Biscay/Basque Government

(Projects DIPE 06/10, UNESCO07/08 and GIU06/87/IT-349–07). NB thanks the Spanish Ministry of Education and Science for a predoctoral scholarship. The authors also thank Petronor, S.A. (Muskiz, Bizkaia, Spain) for a generous donation of hexane.

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