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A convenient approach to the xanthone scaffold by an aqueous aromatic substitution of bromo- and iodoarenes

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ABSTRACT

Unusual displacements of bromides and iodides through nucleophilic aromatic substitution reactions give a direct access to the xanthone core. This sustainable process is based on the use of water as an environmentally friendly solvent.

1. Introduction

The nucleophilic aromatic substitution (S_NAr) reaction is a classic and well established synthetic tool to build a wide range of target molecules, among which pharmaceuticals and diverse drugs can be found.[1] These displacements have been traditionally accomplished under harsh reaction conditions and normally required sufficiently activated aromatic rings (e.g., substituted with preferably more than one nitro group).[2] Besides, the reaction outcome and its rate are strongly related to the nature of the nucleophile strength, the solvent and the leaving-group ability, which normally is considered to be decreasing in the series of F, $NO_2 \gg Cl > Br > I$.[3] Thus, in general, the practical synthetic utility of bromide and iodide displacement in S_NAr processes could be considered relatively limited.[4,2e]

The xanthone skeleton constitutes the core of an important natural and biologically active family of compounds present in higher plants and microorganisms.[5] One of the most employed strategies to access to xanthones involves a S_NAr reaction from conveniently substituted benzophenones. In this context, 2,2′-dihydroxybenzophenones, 2-alkoxy-2′-hydroxybenzophenones and 2,2′-dialkoxybenzophenones have been the substrates of choice.[6] 2-Fluoro and 2-chloro-2′-hydroxybenzophenone derivatives have also given rise to xanthones successfully.[7] On the contrary, nucleophilic substitution of 2-iodo and 2-bromo-2′-hydroxybenzophenone derivatives has never been a general approach to the valuable xanthone skeleton.[8] As in the course of our recent work on the preparation of xanthones through a copper-catalysed intramolecular O-arylation reaction from both 2-bromo and 2-iodobenzophenones we observed the formation of a little amount of cyclised product **1** (10%) in the absence of any copper source (Table 1, entry 1),[9] we decided to study this transformation in detail.

Herein, we wish to report a simple and general procedure for the construction of the xanthone core based on unusual iodide and bromide displacements. In addition, this key transformation is performed in water, a sustainable and very convenient solvent.[10]

2. Results and discussion

As mentioned above we detected the formation of a little amount of the target xanthone **1a** when the reaction was carried out stirring the previously prepared[11] 2-bromobenzophenone **2a** in the presence of 3.5 equiv of TMEDA in water at 120 °C (Table 1, entry 1). Encouraged by this result the reaction was screened with several bases, studying mainly the influence of their strength and amount in the reaction outcome, as shown in Table 1. Water was the only evaluated solvent due to the benefits associated to its use, as non-flammability, easy-handling and environmental benignity.[12]

Considering the typical toxicity and price of nitrogen-containing organic bases, we opted preferably for performing the reactions by employing alkoxides and inorganic cheap bases.

When 2-bromobenzophenone **2a** reacted in the presence of 3 equiv of K_2CO_3 at 120 °C the S_NAr reaction proceeded smoothly, affording the cyclised product in 88% yield (entry 2). A change in the counter ion from potassium to sodium only provided a curious decrease in the yield (from 88 to 76, entries 2 vs 3). The use of weaker bases, such as NaOAc, KOAc or pyridine resulted in the recovery of the unreacted substrate (entries 4 and 5).

From all the hydroxides tested KOH proved superior to both NaOH and $LiOH \cdot H_2O$, delivering target xanthone **1a** in an excellent yield of 92% (entries 9 vs 6–8). Attempts to decrease the reaction temperature and the amount of base were successful, showing

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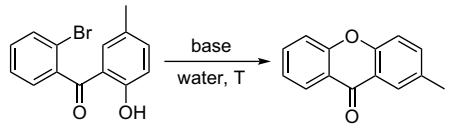
Table 1
Selected assays for the synthesis of xanthone **1a**[a]



2a **1a**

Entry	Base[b]	Equiv	*T* (°C)	Yield[c] (%)
1	TMEDA	3.5	120	10
2	K_2CO_3	3.0	120	88
3	Na_2CO_3	5.0	120	76
4[d]	NaOAc	4.0	120	0
5	py	4.0	120	0
6	$LiOH·H_2O$	4.0	120	85
7	NaOH	2.0	120	73
8	NaOH	3.0	100	79
9	KOH	4.0	120	92
10	KOH	3.0	100	90
11	KOH	2.0	100	93
12	KOH	1.0	100	67
13[e]	KOH	2.0	100	76
14[f]	KOH	2.0	100	93
15	NaO^{t}Bu	3.0	120	97
16	NaO^{t}Bu	3.0	100	95
17	NaO^{t}Bu	3.0	80	73
18	NaO^{t}Bu	2.0	100	97
19[g]	NaO^{t}Bu	1.0	100	93
20	NaO^{t}Bu	0.5	100	69

[a] The reactions were run in distilled water (12 mL/mmol) at the specified temperature and overnight.
[b] TMEDA: *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, py: pyridine.
[c] Yield of isolated product.
[d] The same result was obtained using KOAc.
[e] Dilution (2 mL/mmol) was used.
[f] Dilution (25 mL/mmol) was used.
[g] A lower yield (73%) was obtained with KO^{t}Bu.

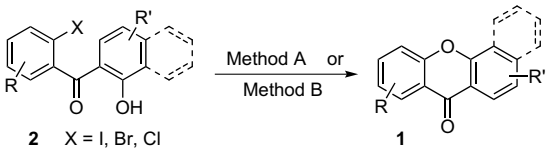
that still good to excellent results could be obtained using 3, 2 and even only 1 equiv of inexpensive KOH at 100 °C in neat water (entries 10–12). When the concentration of the reactants in the aqueous solution was increased the yield diminished to 76% (entries 13 vs 11). However, the use of a more diluted solution apparently did not affect the outcome of the reaction (entry 14). Interestingly, when the more reactive NaO^{t}Bu was used, the reaction proceeded efficiently to render the tricyclic skeleton (entries 15–20), isolating the product in an excellent yield of 93% when only 1 equiv of the base was added (entry 19). Moreover, a still good yield of 69% of xanthone **1a** was obtained when NaO^{t}Bu was employed in substoichiometric amounts (0.5 equiv, entry 20). An additional experiment reducing the temperature to 80 °C was run, but unfortunately the yield decreased to 73% (entries 16 vs 17).

Taking into account all the experimental results it was decided that the best conditions involved stirring the starting material in the presence of either 2 equiv of KOH or only one of Na^{t}OBu in water at 100 °C (Methods A and B, respectively, hereafter). It should be pointed out the ease of the reaction setup, absence of side products and no requirement of an inert atmosphere.

Once having optimised the conditions for the intramolecular S_NAr in aqueous media, a series of 2-iodo, 2-bromo and 2-chlorobenzophenones **2a**–**n**[11] were subjected to them. The results are displayed in Table 2.

As shown in Table 2 excellent results were obtained in the cyclisation processes, regardless the nature of the halogen present in the aromatic moiety. In contrast with the intramolecular copper-catalysed O-arylation reaction,[9] 2-chlorobenzophenone derivatives **2c**, **2e** and **2j** proved to be valuable starting materials in this aqueous S_NAr (entries 3, 5 and 10). 2-Iodo and 2-bromobenzophenone

Table 2
Preparation of a series of xanthones **1**[a]



2 X = I, Br, Cl **1**

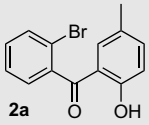
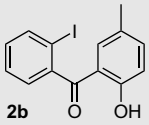
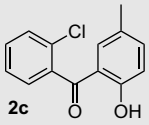
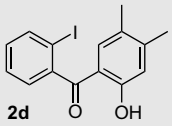
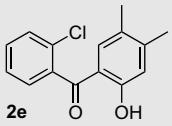
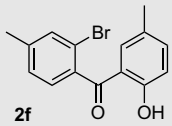
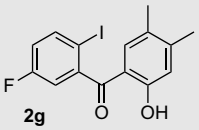
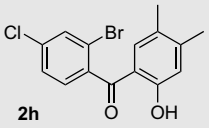
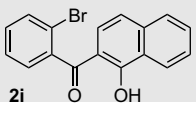
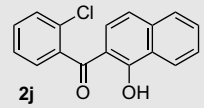
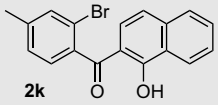
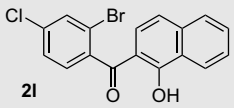
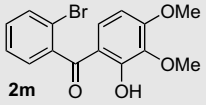
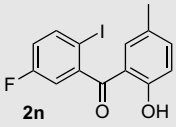
Entry	Substrate	Yield **1**[b] (%)	
		Method A	Method B
1	 **2a**	93	93[c]
2	 **2b**	99	
3	 **2c**	90	92
4	 **2d**	79	
5	 **2e**	91	
6	 **2f**	>99	
7	 **2g**	49	60
8	 **2h**	>99	
9	 **2i**	91	>99

Table 2 (*continued*)

Entry	Substrate	Yield **1**[b] (%)	
		Method A	Method B
10	 **2j**	87	95
11	 **2k**	64	>99
12	 **2l**	86	
13	 **2m**	>99	
14[d]	 **2n**	—	

[a] Method A: 2 equiv of crushed KOH, distilled H_2O (12 mL/mmol) at 100 °C. Method B: 1 equiv of Na^{t}OBu, distilled H_2O (12 mL/mmol) at 100 °C.
[b] Yield of isolated product.
[c] Yield (97%) was obtained using 2 equiv of Na^{t}OBu.
[d] A mixture of inseparable products was observed.

derivatives afforded regioselectively the target tricyclic skeleton in similar and sometimes even better yields to 2-chloro analogues (Table 2, entries 1 and 2 vs 3; 4 vs 5 and 9 vs 10). These relatively surprising results should be outlined, considering the already established order of leaving-group ability in the S_NAr, in which iodides and bromides are the least reactive ones.

Method B was only employed when the yields obtained with Method A were moderate. Although the former method proved superior (entries 2–4, 7, 9–11), we chose KOH due to its lower cost and greater availability. The presence of additional halogens in the substrate was compatible with the reaction conditions (entries 7, 8 and 12), not observing side reactions. However, on the basis of the results displayed in entries 7, 8 and 12, it can be suggested that *m*-Cl substituents activate the reaction and the use of the *p*-fluorinated substrates provokes a significant decrease in the yield is observed. Moreover, the cyclisation reaction did not proceed from 2-iodobenzophenone derivative **2n** (entry 14). The electron-rich 2-bromobenzophenone **2m** rendered the target xanthone in a quantitative yield (entry 13). In the same context of relatively sterically hindered substrates, the reaction conditions were also successful when the hydroxyl group containing moiety was a 1-hydroxynapthalene, obtaining the corresponding tetracycle with excellent yields ranging from 86 to 100% (entries 9–12).

3. Conclusions

In summary, two practical and high yielding methodologies based on S_NAr processes to access to the appealing xanthone framework from the corresponding 2-halo-2′-hydroxybenzophenones are reported. These alternative protocols provided excellent results from non-conventional bromo and iodo derivatives, thus relativising the role of the latter leaving groups. Moreover, several functionalities were easily tolerated in the substrates. Besides, the use of water as solvent makes our methods environmentally friendly and attractive for pharmaceutical purposes.

4. Experimental section

4.1. General remarks

All reagents and solvents were purchased and used without further purification. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in a Bruker AC-300. Chemical shifts are reported in parts per million downfield (d) from Me_4Si. IR spectra were recorded on a Perkin–Elmer 1600 FT infrared spectrophotometer and only noteworthy absorptions are listed. Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F254, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 230–400 mesh ASTM). Drying of organic extracts after work-up of reactions was performed over anhydrous Na_2SO_4. HRMS were measured using a Waters GCT Mass Spectrometer.

4.1.1. General procedure

A screw-capped tube (approximate volume: 18 mL) was charged with 2-haloarylbenzophenone 2 (1 equiv), KOH (2 equiv, Method A) or NaO^{t}Bu (1 equiv, Method B) and water (12 mL/mmol) at room temperature. After closing, the tube was heated to 100 °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 as a white powder.

This general procedure was applied to 2-halobenzoylbenzophenones **2**, providing the following products.

4.1.2. 2-Methylxanthen-9-one[13]

Starting from 2-bromobenzophenone **2a** yields of >99% (*Method A*) and 93% (*Method B*) were obtained.

Starting from the 2-iodoarylbenzophenone **2b** a yield of >99% (*Method A*) was obtained.

Starting from 2-chlorobenzophenone **2c** yields of 90% (*Method A*) and 93% (*Method B*) were obtained.

4.1.3. 2,3-Dimethylxanthen-9-one[14]

Starting from the 2-iodoarylbenzophenone **2d** a yield of 79% (*Method A*) was obtained.

Starting from the 2-chloroarylbenzophenone **2e** a yield of 79% (*Method A*) was obtained.

4.1.4. 2,3-Dimethylxanthen-9-one[9]

Starting from the 2-chloroarylbenzophenone **2f** a yield of >99% (*Method A*) was obtained.

4.1.5. 2-Fluoro-6,7-dimethylxanthen-9-one[9]

Starting from 2-iodobenzophenone **2g** yields of 49% (*Method A*) and 60% (*Method B*) were obtained.

4.1.6. 3-Chloro-6,7-dimethylxanthen-9-one[9]

Starting from the 2-bromoarylbenzophenone **2h** a yield of >99% (*Method A*) was obtained.

4.1.7. 7H-Benzo[c]xanthen-7-one[14]

Starting from 2-bromobenzophenone **2i** yields of 91% (*Method A*) and >99% (*Method B*) were obtained.

Starting from 2-chlorobenzophenone **2j** yields of 87% (*Method A*) and 95% (*Method B*) were obtained.

4.1.8. 10-Methyl-7H-benzo[c]xanthen-7-one[9]

Starting from 2-bromobenzophenone **2k** yields of 64% (*Method A*) and >99% (*Method B*) were obtained.

4.1.9. 10-Chloro-7H-benzo[c]xanthen-7-one[9]

Starting from the 2-bromoarylbenzophenone **2l** a yield of 86% (*Method A*) was obtained.

4.1.10. 3,4-Dimethoxyxanthen-9-one[9]

Starting from the 2-bromoarylbenzophenone **2m** a yield of >99% (*Method A*) was obtained.

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Supplementary data

Typical experimental procedures, including spectroscopic and analytical data for all the new intermediates along with NMR spectra of the new compounds. This material is available free of charge via ScienceDirect. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.05.021.

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