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Alternative simple and effective synthesis of (di)benzoxanthones and their functions toward fluorescent dyes

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ABSTRACT

(Di)benzoxanthones possessing additional benzene units on one or both sides of xanthone were prepared via dehydration of the corresponding dihydroxybenzophenone, where a catalytic amount of K_2CO_3 dramatically increased the yields. Chemical transformations of the versatile carbonyl groups of (di)benzoxanthones could derive fluorescent materials.

1. Introduction

Xanthone skeletons, which commonly occur in natural products,[1] exhibit various pharmacological activities (e.g., anti-cancer and anti-bacterial properties)[2] and in the medicinal chemistry field, are frequently valued as effective pharmacophores.[3] Additionally, xanthone skeletons frequently display fluorescent responses, which have facilitated the development of fluorescent dyes derived from xanthone as a key fragment.[4] Consequently, much effort has been devoted to effectively synthesize xanthones. Larock et al. have constructed various xanthones though arynes and C–H activation.[5] Recently, xanthones have been constructed under mild conditions using palladium-catalyzed oxidative double C–H carbonylation of biarylethers.[6] Although many synthetic routes have been reported, cyclization from the benzophenone possessing the proper functional groups on the scaffolding 2,2′-positions remains the most common.

Xanthone synthetic routes are classified roughly into two groups according to the functional groups on the 2,2′-positions: (1) cyclization from 2-hydroxy-2′-halogen or alkoxy benzophenones under basic conditions though *ipso*-substitution[7] and (2) dehydrative cyclization from 2,2′-dihydroxybenzophenones under (mainly) harsh conditions. The latter route is further divided according to the reaction conditions. Dehydrative cyclization has been reported to occur under neutral conditions at high temperature in water using a sealed tube[8] or SiO_2 as a dehydration reagent,[9] as well as under acidic conditions using a catalytic amount of H_2SO_4[10] or melting pyridinium hydrochloride.[4d,8b] Additionally, there are a few cases where dehydrative cyclization occurs under basic conditions using ethanolic KOH or a large excess of sodium acetate.[11]

On the other hand, our research focuses on colorimetric molecular recognition based on phenolphthalein with two crown loops. To date, we have successfully visualized features of guest molecules, such as chirality, shape, and size.[12] In particular, our work has targeted spermidine and spermine, which are biogenic polyamines, to develop a practical method to determine the spermidine level in living cells.[13] We aim to change our molecular recognition system from a color-response type to a fluorescent-response type. We recently reported the exhaustive syntheses of naphthofluoresceins possessing additional benzene units on one or both sides of fluorescein, and revealed that some naphthofluoresceins exhibit fluorescent emissions in the near infrared region (>700 nm) with large Stokes shifts and humble quantum yields.[14]

To improve the quantum yields of the derivatives, we selected (di)benzoxanthone skeletons as key intermediates due to the versatility of the carbonyl groups of (di)benzoxanthones. These carbonyl groups can be converted into other functional groups through Wittig reactions, organometallic reagents, etc. to afford a variety of fluorescent molecules within a few reaction steps.[4]

Herein, we describe the exhaustive syntheses of nine (di)benzoxanthones from their corresponding 2,2′-dihydroxybenzophenones in the presence of a catalytic amount of K_2CO_3, as well as their optical properties.

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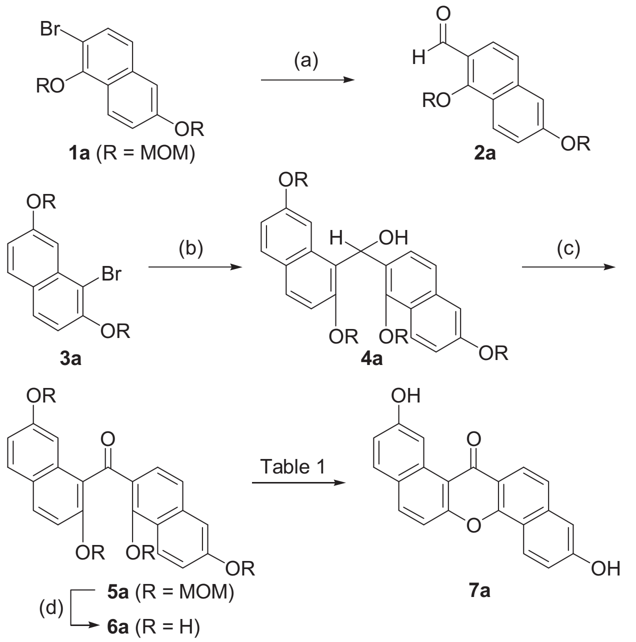
2. Results and discussion

Scheme 1 shows the synthesis of dibenzoxanthone **7a**. Bromonaphthalene **1a**[14] was lithiated by *n*-BuLi and trapped with DMF to afford aldehyde **2a** in 81% yield. The corresponding coupling partner **3a** was treated with *n*-BuLi and allowed to react with aldehyde **2a** to give **4a** in 93% yield. Dibenzylic alcohol **4a** was oxidized by MnO_2 in 72% yield. HCl in dioxane was then used to remove the four MOM groups in compound **5a**, producing cyclization precursor **6a** in 96% yield. The other precursors were synthesized by the same procedure in moderate to good total yields (see Supplementary data). Table 1 shows the results of different reaction conditions on the intramolecular dehydration from precursor **6a** to dibenzoxanthone **7a**.



Scheme 1. Synthetic route for dibenzoxanthone **7a**. (a) *n*-BuLi, DMF, 81% yield; (b) *n*-BuLi, **2a**, 93% yield; (c) MnO_2, 72% yield; (d) HCl in dioxane, 96% yield.

Table 1
Dehydration from **6a** to **7a**

Entry	Solvent	Additive (equiv)	Temp (°C)	Time (h)	Yield of **7a** (%)
1[8]	H_2O	—	150[a]	9	0.3[b]
2[9]	—	SiO_2	40	21	No reaction
3[10,14]	$MeSO_3H$	—	50	3.5	Decomposed
4[11b,c]	EtOH	KOH (1.0)	Reflux	9	Mixture
5[11e]	CH_3CN	K_2CO_3 (3.0)	Reflux	9	Mixture
6[4d,8b]	Py·HCl[c]	—	150	9	61
7[11d]	H_2O	AcONa (10)	Reflux	9	21
8	H_2O	K_2CO_3 (0.1)	Reflux	9	62
9	H_2O	K_2CO_3 (0.1)	150[a]	9	99
10	H_2O	Li_2CO_3 (0.1)	150[a]	9	93
11	H_2O	Na_2CO_3 (0.1)	150[a]	9	99
12	H_2O	Rb_2CO_3 (0.1)	150[a]	9	96
13	H_2O	Cs_2CO_3 (0.1)	150[a]	9	96
14	H_2O	$(^n\text{Bu})_4\text{NOH}$ (0.1)	150[a]	9	85

[a] Sealed tube condition.
[b] Yield of **7a** calculated based on the integral intensity of ^{1}H NMR.
[c] Pyridinium hydrochloride.

Dehydration in a sealed tube with neutral water and high temperature (150 °C),[8] which are the standard conditions to form the xanthone skeleton, did not proceed, and only a small amount of desired **7a** was detected by NMR (estimated in ca. 0.3% yield, entry 1). Similarly, the reaction did not occur using SiO_2 treatments (entry 2),[9] and cyclization under acidic conditions was not fruitful because several fragmental products, such as 2,7-dihydroxynaphthalene (8% yield) and 1,6-dihydroxy-naphthalene-2-carboxylic acid (17% yield) were obtained instead of desired compound **7a**, (entry 3).[10,14] These data indicate that in the case of compound **6a**, a retro Friedel–Crafts reaction predominantly occurs instead of the desired cyclization under acidic conditions. It is interesting to note that in the case of cyclization of compound **6d**, which is a structural isomer of **6a**, these reactions proceed smoothly under identical conditions to give corresponding dibenzoxanthone **7d** in quantitative yield. In entries 4[11b,c] and 5,[11e] which are from the literature, cyclization under basic conditions in an organic solvent was applied to give an inseparable and complicated compound mixture. In contrast, reactions under basic conditions in water[11d] or molten pyridinium hydrochloride[4d,8b] produced desired **7a** in moderate yields (entries 6 and 7). Because a promising result was obtained in the presence of K_2CO_3 (0.1 equiv) in water (entry 8), we modified the reaction conditions. Thus, the reaction was performed at 150 °C using a sealed tube, which increased the yield of **7a** to 99% (entry 9). Almost no influences of the counter cations (including quaternary ammonium cation) were observed (entries 9–14). Based on these observations, we estimate the conditions in entry 9 (0.1 equiv of K_2CO_3, water, 150 °C) are the most appropriate. It is especially noteworthy that the product was easily isolated from the reaction mixture; filtration isolated cyclized dibenzoxanthone **7a** from an acidified aqueous solution in an extremely pure form without chromatographic purification.

With the optimal reaction conditions in hand, we then studied the generality of substrates for the reaction using other dihydroxybenzophenones **6b–i** (Fig. 1). Intramolecular dehydration

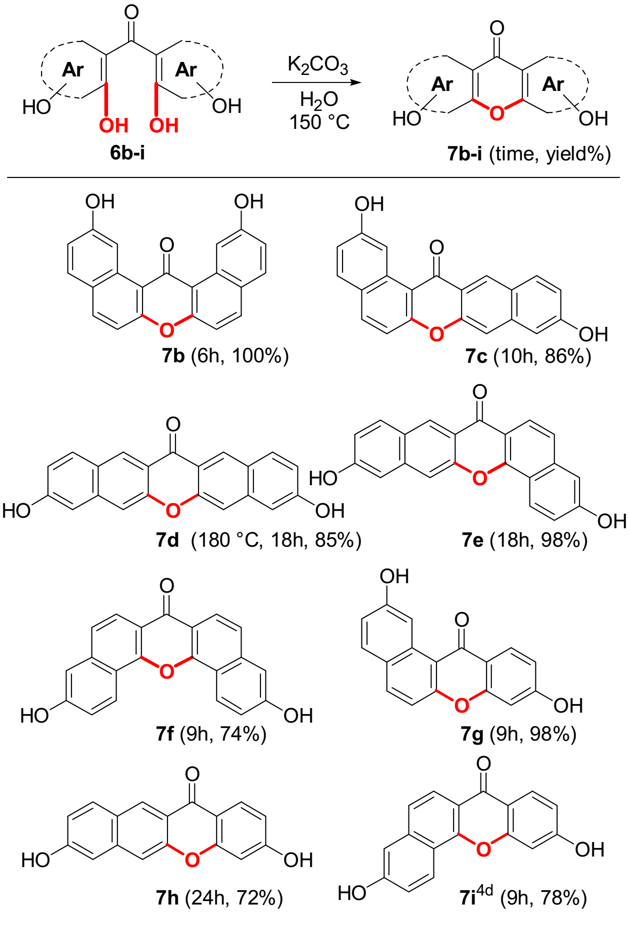


Fig. 1. Syntheses of (di)benzoxanthones **7b–i**.