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A photo-induced C–O bond formation methodology to construct tetrahydroxanthones†

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A metal-free, photo-induced C–O bond formation methodology was developed to construct tetrahydroxanthones. This mild and efficient methodology was based on intramolecular oxygen trapping of the reactive species produced by photolytic activation of a C–Cl bond. We believe this method could be used in the synthesis of related xanthone-type natural products.

Xanthone-type natural products exist widely in fungi and bacteria as secondary metabolites.[1] These molecules have increasingly attracted the attention of synthetic chemists and biochemical research groups because of their potential as anticancer or antibiotic agents.[1c] In fact, natural xanthones and their derivatives, especially polycyclic xanthones, have been termed "privileged structures" because of their broad spectrum of biological activities.[2] The core structure of most members of the large xanthone family contains either fully unsaturated aromatic rings (A and C rings) or partially hydrogenated rings, including di-, tetra-, or hexahydro derivatives (C ring) (Fig. 1). The xanthone family can be divided into structural subgroups of monomers (diversonol and blennolide C),[3] dimers (puniceaside B)[4] and polycyclic xanthones (cervinomycin A_2[5] and kibdelone C[6]). Despite being in different oxidation states, biogenetically related xanthones were occasionally discovered from the same natural source, which indicated that they should share the same biosynthetic pathway. The synthesis of polycyclic xanthones has been proven to be challenging because of their highly oxygenated and angular hexacyclic structures such as basic aromatized xanthones or tetrahydroxanthone rings. In 1989, Kelly and co-workers reported the first synthesis of a fully aromatized polycyclic xanthone, cervinomycin A_2, using a convergent approach.[7] An even greater synthetic breakthrough for this family of natural products came in 2011, when both the Porco[8] and Ready[9] groups achieved the total synthesis of kibdelone C,

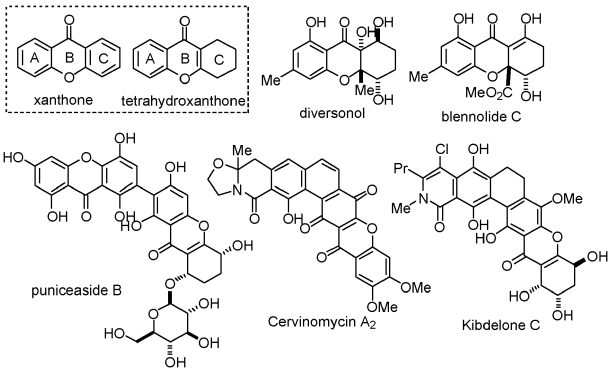

Fig. 1 Xanthone-type natural products.

a partially hydrogenated polycyclic tetrahydroxanthone. Since our research group is interested in the synthesis of bioactive natural products with anticancer potential,[10] we wished to develop an efficient approach to construct tetrahydroxanthones in order to create the basic skeleton for subsequent syntheses of polycyclic xanthones. As a first step, we report here the construction of tetrahydroxanthones involving a photo-induced C–O bond formation. We believe this protocol will be useful for synthesis of xanthone-type natural products for medicinal chemistry.

Normally, transition metals[11a–d] and Michael addition[11a,e,f] under basic conditions are used to catalyze C–O bond formation during construction of tetrahydroxanthones. In 2011, Shipman and co-workers reported elegant Pd-catalyzed formation of C–O and C–C bonds to construct 7-substituted tetrahydroxanthones in a single step (Scheme 1).[12] However, this procedure may be too harsh for constructing tetrahydroxanthones with sensitive functional groups often required for synthesis of natural products. Therefore we wished to achieve a similar reaction but under milder conditions at neutral or basic pH. Literature searches revealed that photo-induced C–halogen bond activation can be used to produce cations[13] that can undergo the nucleophilic substitutions required for the synthesis of tetrahydroxanthones. Inspired by this method, we envisioned to construct the C–O bond of tetrahydroxanthones by trapping the cation or related

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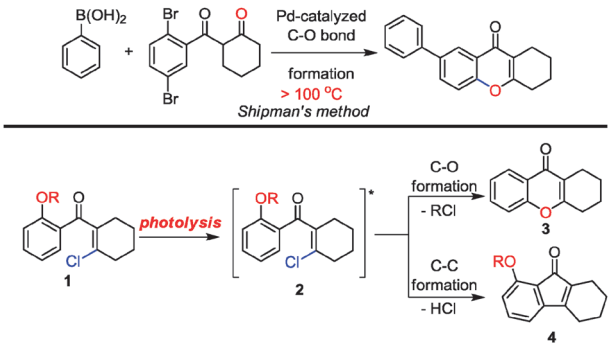
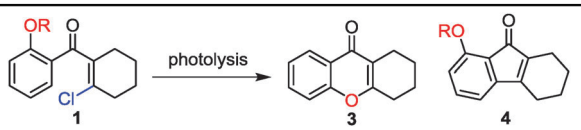


Scheme 1 Formation of tetrahydroxanthones by photolysis.

reactive spices generated by photochemistry. We designed substrate **1** containing all the reactive elements, and reasoned that selective activation of the enone and the C–Cl bond would give the photo-excited intermediate **2**, which could be trapped by a nucleophile such as oxygen to yield **3**. In addition, **2** could undergo intramolecular cyclization to give fluorenone **4**.

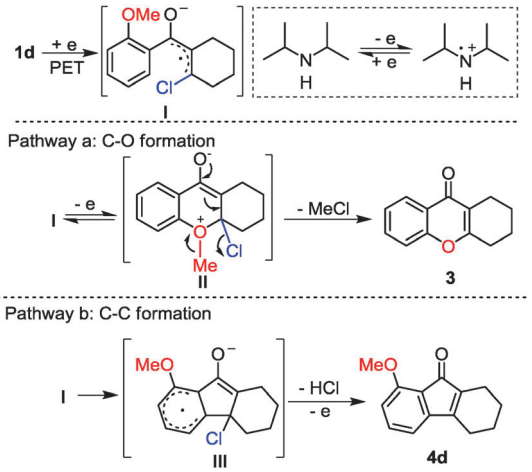
To test our rational design, we prepared five substrates with different protecting groups on phenol (**1a–f**) and treated them with UV light at 300 nm. UV irradiation of a solution of **1a–c** and **1e** (0.01 mol L^{-1}) in acetonitrile caused the substrates to decompose (entries 1–3 and 5, Table 1). To our delight, when we irradiated **1d** and **1f** under the same conditions, the desired tetrahydroxanthone **3** was obtained in about 19% yield (entries 4 and 6). This suggests that photolysis allowed the intramolecular oxygen trapping under these neutral conditions, albeit to a limited extent. We extensively screened reaction conditions and found that adding a base such as diisopropylamine (1.0 equiv.) dramatically improved the reaction efficiency. Thus irradiation of **1a–c** in acetonitrile in the presence of diisopropylamine smoothly gave the corresponding fluorenones **4a–c** without formation of **3** (entries 7–9). We reasoned that the intramolecular C–C bond formation in these reactions was facilitated by restricted rotation of the aromatic ring

Table 1 Photo-induced C–O bond formation



Entry	R	Time	Base	Conversion[a] (%)	Ratio (3 : 4)[a]	Yield (3)[a]	Yield (4)[a]
1	H, **1a**	8.5 h	—	100	—	N.D.[c]	N.D.[c]
2	TBS, **1b**	4 h	—	100	—	N.D.[c]	N.D.[c]
3	Ac, **1c**	5.5 h	—	100	—	N.D.[c]	N.D.[c]
4	Me, **1d**	2 h	—	88	—	19%[b]	N.D.[c]
5	Bn, **1e**	2.5 h	—	100	—	N.D.[c]	N.D.[c]
6	MOM, **1f**	2 h	—	100	—	17%	N.D.[c]
7	H, **1a**	4 h	$^{i}Pr_2NH$[e]	84	—	N.D.[c]	76%[b]
8	TBS, **1b**	40 min	$^{i}Pr_2NH$[e]	100	—	N.D.[c]	48%
9	Ac, **1c**	40 min	$^{i}Pr_2NH$[e]	100	—	N.D.[c]	67%
10	Me, **1d**	40 min	$^{i}Pr_2NH$[e]	100	5.6 : 1	62%	11%
11[d]	Bn, **1e**	50 min	$^{i}Pr_2NH$[e]	100	1 : 2.5	15%	38%
12	MOM, **1f**	50 min	$^{i}Pr_2NH$[e]	100	1 : 3	13%	40%

[a] All were determined by ^{1}H NMR crude analysis using CH_2Br_2 as an internal standard, unless noted. [b] Based on conversion. [c] Not detected. [d] 17% yield of **1a** observed by ^{1}H NMR. [e] 1.0 equiv. $^{i}Pr_2NH$ was added.



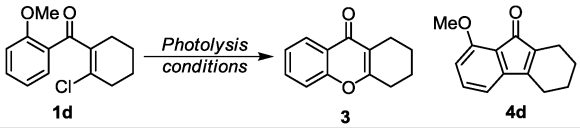
Scheme 2 The proposed mechanism of the photolysis.

due to hydrogen bonding (**1a**) or the bulky TBS group (**1b**). The electron-withdrawing Ac group in **1c** decreased the nucleophilicity of oxygen, suppressing C–O bond formation. Electron-donating protecting groups, such as Me, Bn and MOM (**1d–f**), facilitated the formation of both **3** and **4** (entries 10–12). Remarkably, irradiating **1d** gave **3** and **4d** (ratio = 5.6 : 1) in 73% combined yield. The crude NMR spectrum of this reaction was clean, indicating that the added base plays a major role in the photolysis.

The proposed mechanism of this photolysis is shown in Scheme 2. We speculated that a photoelectron transfer (PET) from diisopropylamine converted **1d** to its corresponding radical anion **I**,[14] which cyclized to form **3** or **4d** through the C–O bond (pathway a) or C–C bond formation (pathway b), respectively. A second electron transfer from **I** followed by intramolecular oxygen trapping led to intermediate **II**. The release of volatile MeCl drived the photolysis forward to give **3** (pathway a). Intermediate **I** could also be cyclized directly to form **III** and eliminated to give **4d** (pathway b). We therefore predicted that the methoxy group on **1d** would make it the best substrate for photo-induced C–O bond formation.

We optimized the reaction conditions for the photolysis of **1d** by extensively screening solvents, bases and light sources (Table 2, see details in the ESI†). Addition of the tertiary amine triethylamine (1.0 equiv.) gave tetrahydroxanthone **3** in 42% yield (entry 1, Table 2). Using tetramethylpiperidine (TMP) as the base led to formation of **3** in 66% yield, with minor amounts of **4d** (9% yield). Using other solvents such as dichloroethane, tetrahydrofuran, toluene or dimethylformamide did not improve the yield (entries 3–6, Table 2). Surprisingly, using water as a co-solvent dramatically improved the yield, using acetonitrile–H_2O (9 : 1, v/v) as a co-solvent giving the best results (entry 7, Table 2) as well as a stoichiometric amount of TMP as the base (5.0 equiv.; entry 12, Table 2). Using this solvent system, we screened several bases (diisopropylamine, triethylamine, DABCO and K_2CO_3), none of which improved the yield (entries 8–11, Table 2). Irradiating the reaction system with 254 or 366 nm light gave yields similar to those obtained with 300 nm light (entry 13, Table 2), although a longer reaction time was required when 366 nm light was used (entry 14, Table 2).

Table 2 Condition screening of photo-induced C–O bond formation



1d 3 4d

Entry	λ (nm)	Solvent	Base[b]	Time	Conversion (%)	Yield 3[d] (%)	Yield (4d)[d]
1	300	CH_3CN	NEt_3	40 min	100	42	Trace
2	300	CH_3CN	TMP	40 min	100	66	9%
3	300	DCE	TMP	40 min	100	60	22%
4	300	THF	TMP	40 min	100	14	Trace
5	300	Toluene	TMP	40 min	100	32	20%
6	300	DMF	TMP	40 min	100	19	Trace
7	300	$CH_3CN:H_2O$[a]	TMP	40 min	100	82	5%
8	300	$CH_3CN:H_2O$[a]	$^iPr_2NH$	40 min	100	74	6%
9	300	$CH_3CN:H_2O$[a]	NEt_3	40 min	100	31	Trace
10	300	$CH_3CN:H_2O$[a]	DABCO	40 min	100	78	9%
11	300	$CH_3CN:H_2O$[a]	K_2CO_3	50 min	100	69	Trace
12	300	$CH_3CN:H_2O$[a]	TMP[c]	40 min	100	85	4%
13	254	$CH_3CN:H_2O$[a]	TMP	40 min	100	79	5%
14	366	$CH_3CN:H_2O$[a]	TMP	3 h	100	84	8%

[a] Acetonitrile : H_2O = 9 : 1, (v/v). [b] 1.0 equiv. base was added, unless noted. [c] 5.0 equiv. TMP was added. [d] All the reaction yields were determined by ^1H NMR crude analysis using CH_2Br_2 as an internal standard, unless noted.

Next we explored the stability of both **3** and **4d** under the photolytic conditions used to generate both compounds from **1d**. We set up the photolysis reaction under the optimized conditions and monitored its progress by NMR spectroscopy. As shown in Fig. 2, photolysis of **1d** was normally complete within 40 min. The highest yields of both **3** and **4d** appeared in around 20 min, after which the yields slowly decreased. These results suggest that both **3** and **4d** are photo-sensitive, with **4d** decomposing slightly faster than **3**. We also tested the photo-stability of compound **3** in the presence and absence of a secondary amine (TMP). Under the same photolytic conditions, we found that TMP does not affect the stability of **3**, which decomposes at the same rate as in the normal reaction system.

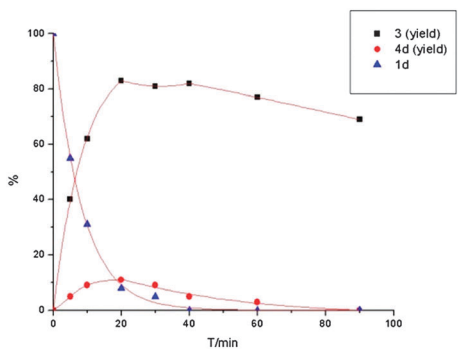
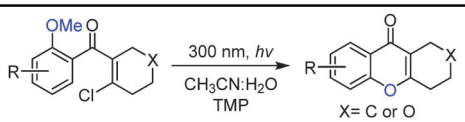
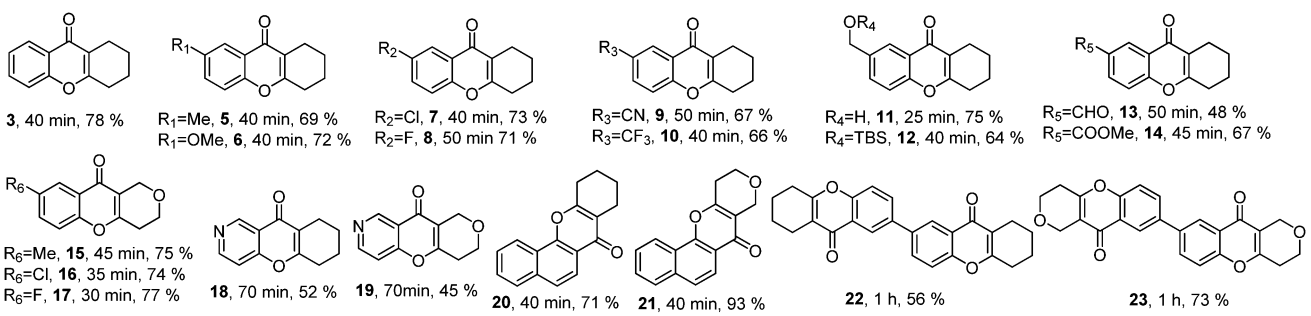


Fig. 2 A curve of the progress of the photolysis.

We then investigated the scope of this photo-induced C–O bond formation to construct tetrahydroxanthones under the optimized conditions. Firstly, we found that the electron density of the aromatic ring did not affect the reaction: both electron-donating (Me–, –OMe) and -withdrawing (–Cl, –F, –CN, $–CF_3$) groups on the phenyl rings worked well under the optimized basic conditions (**5–10**, Table 3). Subsequently, we tested the substrates with different functional groups. To our delight, we found that this photolysis tolerated hydroxyl, aldehyde, ester and acid-sensitive groups such as OTBS, producing corresponding tetrahydroxanthones in good yields (**11–14**, Table 2). These results suggested that this photolysis should be a sufficiently mild method and provide a platform to build xanthone-based natural products functionalized with sensitive functional groups, allowing the synthesis of diverse potential anticancer compounds. When the cyclohexene ring of the substrates was exchanged with a pyran ring, corresponding dihydropyrano-containing xanthones were obtained (**15–17**, Table 2). We also explored hetero-aromatic rings instead of phenyl rings in this photolysis. We were pleased to find that substrates containing pyridines (**18** and **19**) reacted smoothly in the photolysis, furnishing the fused heterocycles in good yield. We then tried to use this methodology in the synthesis of the core skeleton of xanthone containing natural products. Interestingly, the basic skeletons of polycyclic xanthones, **20** and **21**, which involve naphthyl moieties, were obtained in good to excellent yield. Dimeric tetrahydroxanthones could also be achieved using similar photolytic transformation. **22** and **23** which share similar structural features of puniceaside B were constructed by this photolysis method. To the best of our knowledge, this is the first report on photo-induced C–O bond formation for constructing tetrahydroxanthone under neutral or basic conditions.

Table 3 The reaction scope of the photo-induced tetrahydroxanthone formation





To demonstrate the reliability and practicability of this photolysis method, we irradiated **1d** in the gram-scale (1.3 g, 5.2 mmol) under the optimized conditions and comparable yield (80% isolated yield) was obtained. We also scaled up the reaction with **S7** (1.2 mmol) and the photolysis efficiently provided **8** in 86–90% yield, even better than that obtained in the small scale reaction (see details in the ESI†).

In summary, we have developed a photo-induced C–O bond formation methodology for the construction of tetrahydroxanthones. The photolytic conditions and scope of the photolysis were systematically studied. We found that this mild, metal-free reaction proceeds under neutral or basic conditions at room temperature. Various substrates containing electron rich or deficient aromatic rings and different functional groups tolerate this photolysis well, giving good to excellent yields. We also preliminarily used this methodology in the construction of the basic skeleton of xanthone containing natural products. We are exploring the total synthesis of kibdelone C and structurally related polycyclic xanthones using this method.

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