Synthetic Methods

Synthesis of Functionalized Salicylate Esters and Amides by Photochemical Acylation**

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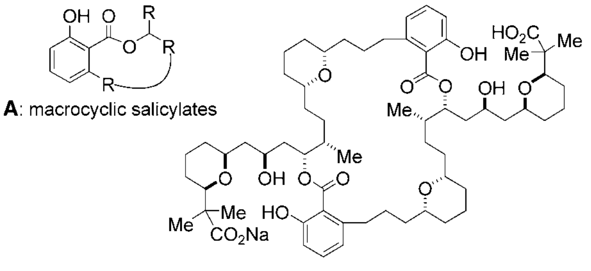
Ortho-substituted salicylate esters (**A**) are an integral subunit of various important natural products.[1] Often, their formation through acylation poses a problem for which no general solution has been formulated.[1] Indeed, acylation is impeded by a combination of increased electron density and steric hindrance (*ortho*-substitution) at the acyl carbon center. This problem is circumvented through reactivity umpolung with Mitsunobu-type chemistry, but is limited to relatively unhindered alcohol substrates.[2] Alternative approaches include alcohol activation by alkoxide formation,[3,4] high-temperature trans-esterification with salicylate cyanomethyl esters,[5] Trost–Chisholm lactonization,[6] or late-stage de novo aryl synthesis.[7] However, numerous failed attempts to introduce an *ortho*-functionalized salicylate ester during our synthetic program for **1** (SCH 351448) required us to address the limitations of current methodology and formulate alternative approaches.[8]



A: macrocyclic salicylates

1 (SCH 351448)

In search of useful reactivity patterns, we settled on the exploration of quinoketenes as potential highly reactive electrophylic salicylate equivalents. Quinoketene **C** (R = H) has been implicated as a reactive intermediate during various thermolytic and photochemical processes and was spectroscopically characterized at low temperatures in glassy or argon matrices.[9] Of the various reaction manifolds to quinoketene,[9] we were most inspired by the photolysis of 2-phenyl-benzo[1,3]dioxin-4-one (**B**, R = H) which has led to the first observation of quinoketene **C** (R = H) in solution at

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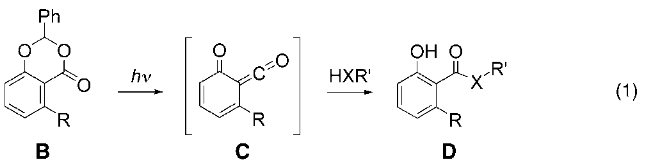
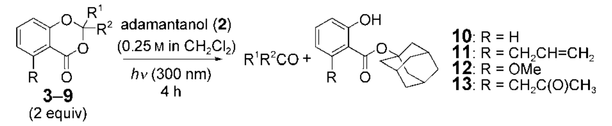
room temperature [Eq. (1)].[10] In the same report, Tidwell and co-workers also detailed quantitative reactivity studies



and proposed a pseudopericyclic transition state for the capture of **C** ($R = H$) with water, methanol, and diethylamine.[10a] Despite this theoretical and mechanistic interest, and contrary to the situation with α-oxoketenes,[9b] the synthetic exploitation of quinoketenes for the formation of salicylate esters and amides remains largely unexplored.[11] Herein we report a general and high-yielding protocol for the synthesis of sterically hindered *ortho*-substituted salicylates through photolysis of previously unexplored *ortho*-substituted benzodioxinones in the presence of sterically hindered alcohols, phenols, and anilines [Eq. (1), $R \neq H$], and for the first time we shed some light on the mechanism and structural requirements for the photochemical decomposition of benzodioxinones.

Initial efforts to develop the photochemical acylation as a preparative method for the formation of salicylate esters were promising. Using a set of optimized conditions, we found that irradiating ($\lambda = 300$ nm) a solution that contained the parent 2-phenyl-benzo[1,3]dioxin-4-one (**3**) and 1-adamantanol (**2**) provided 1-adamantyl salicylate (**10**) in 76% yield (Table 1, entry 1).[12] More importantly, *ortho*-substituted salicylate esters **11**–**12** are similarly accessible in high yields through photochemical acylation with *ortho*-substituted benzodioxinones **4**–**6** (entries 2–4). In contrast, heating a mixture of benzodioxinone **4** and 1-adamantanol (**2**) in toluene at 110 °C for 3 hours resulted in complete recovery of starting materials, whereas reaction of benzodioxinone **9** with the adamantanyl-derived sodium alkoxide (**2**, sodium hexamethyldisilazide (NaHMDS), THF) gave a 1:1.5 mixture of the desired salicylate **11** and the corresponding styryl double-bond isomer (not shown) in 25% combined yield. Particularly noteworthy is the formation of the *ortho*-(2-oxopropyl)-substituted salicylate **13** in 80% yield which occurs without a trace of formation of isocoumarin (entry 5)—a reaction pathway that is difficult to avoid with more conventional acylation methods, underscoring the mild conditions of the photochemical alternative.[13]

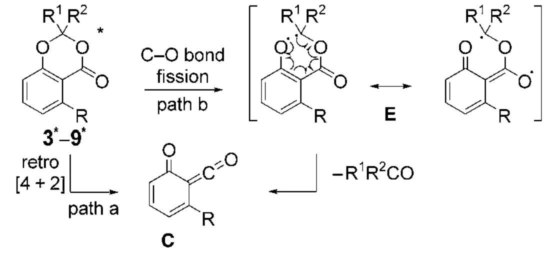
Table 1: Photochemical acylation of 1-adamantanol (**2**) with benzodioxinones **3**–**9**.



Entry	Substrate	R/R^1/R^2	Product	Yield [%]
1	**3**	H/H/Ph	**10**	76
2	**4**	CH_2CHCH_2/H/Ph	**11**	81
3	**5**	CH_2CHCH_2/Ph/Ph	**11**	85
4	**6**	OMe/Ph/Ph	**12**	77[a]
5	**7**	CH_2COMe/H/Ph	**13**	80
6	**8**	OMe/-$(CH_2)_4$-	**12**	6[b]
7	**9**	CH_2CHCH_2/Me/Me	**11**	< 5[b]

[a] Yield after stirring the reaction mixture with K_2CO_3/MeOH.[20] [b] Benzodioxinones **8** and **9** were recovered in ≥ 80% yield.

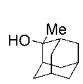
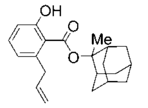
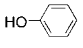
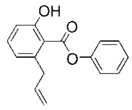
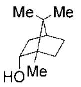
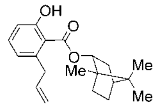
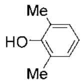
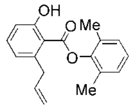
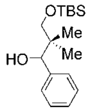
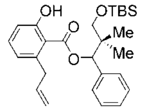
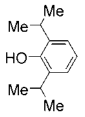
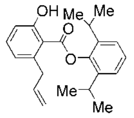
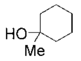
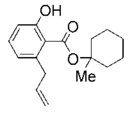
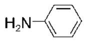
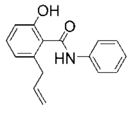
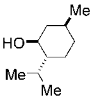
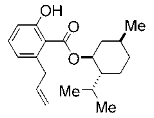
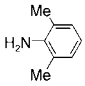
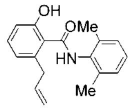
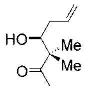
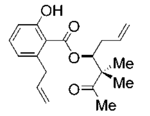
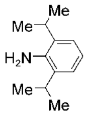
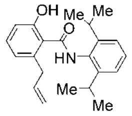
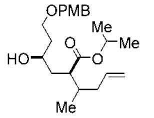
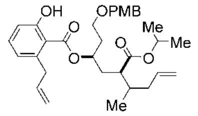
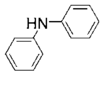
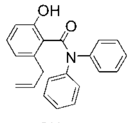
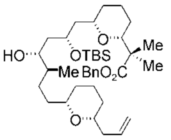
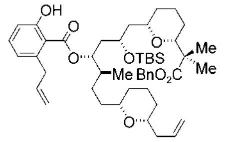
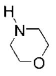
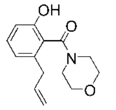
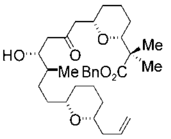
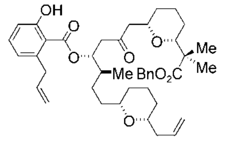
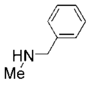
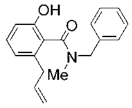
Two alternative pathways can be formulated for the photochemical fragmentation of benzodioxinones to quinoketenes **C** (Scheme 1). One potential pathway features a concerted photochemical [4+2] cycloreversion to generate **C** directly from an excited singlet state (path a). Alternatively, a homolytic C–O bond fission from an excited triplet state would produce a biradical intermediate **E**, followed by a thermal fragmentation to **C** (path b). The following observation provided some insight: 2,2-dialkyl-substituted benzodioxinones **8** ($R^1 = R^2 = (CH_2)_4$) and **9** ($R^1 = R^2 = Me$) were very poor photolysis substrates (Table 1, entries 6–7), despite exhibiting UV/Vis absorbance spectra that were virtually indistinguishable from **6** and **4**/**5** respectively.[14] These results are best explained by invoking biradical intermediate **E** (path b), which is significantly better stabilized by phenyl substitution than by alkyl substitution.[15] The relative quantum yields (φ) for the disappearance of benzodioxinone **4** and concomitant appearance of benzaldehyde at 300 nm were estimated as 0.64 and 0.58, respectively, relative to a benzophenone/benzhydrol actinometer ($\varphi = 0.68$) under identical conditions.[14,16] Our structure–photoactivity studies described above are revealing and provide a guiding principle for the orthogonal exploitation of photoactive and photosilent benzodioxinones.[17]



Scheme 1. Mechanistic considerations.

The results presented in Table 2 demonstrate the broad scope of the photochemical acylation reaction. A wide range of sterically hindered alcohols (**14a**–**i**) are acylated with *ortho*-allyl-substituted benzodioxinones **4** and **5** to provide acceptable yields of salicylate esters **15a**–**i** with broad functional group compatibility (silyl and *p*-methoxybenzyl ethers, ester, aryl, ketone, and olefin functionality). Particular examples include the formation of salicylate esters **15h** and **i** (Table 2), a key transformation in our approach[8a] to SCH 351448 (**1**) that has eluded us with other methodologies. The efficient photochemical acylation of *anti*-β-isopropanoyloxy alcohol (**14g**) represents an alternative approach to a key fragment **15g** in our synthesis of salicylihalamides.[18] On the basis of these results and in line with the proposed pseudopericyclic transition state,[10a] this reaction appears to be less sensitive to steric bulk in the alcohol than classical acylation reactions.[19]

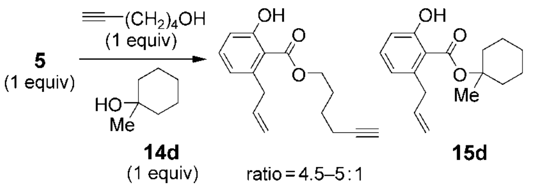
Table 2: Photochemical acylation of alcohols **14a–i**, phenols **16a–c**, anilines **18a–d**, and amines **20a** and **b** with benzodioxinones **4** and/or **5**.[a]

Substrate		Benzodioxinone	Product		Yield [%][b]	Substrate		Benzodioxinone	Product		Yield [%][b]
	**14a**	4 5		**15a**	72[c] 62		**16a**	4 5		**17a**	81 85
	**14b**	4 5		**15b**	76[d] 73		**16b**	4 5		**17b**	82 79
	**14c**	4 5		**15c**	47[d] 61		**16c**	4 5		**17c**	80 83
	**14d**	4		**15d**	73		**18a**	5		**19a**	70[e]
	**14e**	4		**15e**	85		**18b**	5		**19b**	73[e]
	**14f**	5		**15f**	61 (72)[e]		**18c**	5		**19c**	79[e]
	**14g**	5		**15g**	75[e,f]		**18d**	5		**19d**	78[e]
	**14h**	4 5		**15h**	48 45		**20a**	5		**21a**	64[e]
	**14i**	5		**15i**	65[f]		**20b**	5		**21b**	73[e]

[a] Photolysis ($\lambda = 300$ nm) of benzodioxinone (2 equiv) in the presence of alcohol/amine (1 equiv, 0.25 M) in CH_2Cl_2 at RT for 4 h. See Experimental Section and Supporting Information for details. TBS = *tert*-butyldimethylsilyl, PMB = *p*-methoxybenzyl, Bn = benzyl. [b] Isolated yields of chromatographically pure material. [c] Twofold excess of alcohol. [d] 3 equivalents of **4**. [e] Yield obtained after stirring the reaction mixture with K_2CO_3/MeOH.[20] [f] Alcohol was recovered in 17%.

For more quantitative information, we performed a competition experiment between 5-hexyn-1-ol and 1-methyl-cyclohexanol (**14d**) for photoacylation with benzodioxinone **5** [Eq. (2)]. ^{1}H NMR spectral analysis of the crude reaction mixture revealed an approximately 5:1 mixture of primary/tertiary alcohol derived salicylate esters.

Phenols (**16a–c**) and anilines (**18a–d**) are particularly good substrates for photoacylation, providing substituted salicylate esters **17a–c** and anilides **19a–d** which are not accessible by Mitsunobu methodology (Table 2): this is dramatically illustrated by the efficient formation of *o,o'*-substituted benzoates of 2,6-(iPr)$_2$PhOH (**16c**), 2,6-(iPr)$_2$PhNH$_2$ (**18c**), and Ph$_2$NH (**18d**; Table 2, products **17c** and **19c** and **d**, respectively) under essentially neutral conditions. In a control experiment, heating a solution of aniline and benzodioxinone **5** or **9** in toluene in a sealed vial at 110 °C for 3 h resulted in complete recovery of unconverted starting materials. Finally, secondary amines (**20a** and **b**) also participate as nucleophiles in the photoacylation (Table 2, products **21a** and **b**).[20]



(2)

In conclusion, we have developed a general method for the synthesis of functionalized salicylic esters and amides by photolysis of *ortho*-functionalized 2-phenyl-benzo[1,3]dioxin-4-ones in the presence of alcohols, phenols, amines, and anilines. This reaction occurs under essentially neutral conditions, yet efficiently engages a very wide range of acylation substrates, including sterically hindered nucleophiles that are inert to other acylation methods.[21] The present study also defines the structural requirements for efficient photolysis of benzodioxinones to quinoketenes. Applications toward natural product synthesis and exploration of other reactivity modalities of quinoketenes generated in situ will be reported in due course.

Experimental Section

Procedure A (Table 1, entries 1–3 and 5–7; Table 2, **15a–e**, **15h** and **i**, and **17a–c**): An oven-dried borosilicate test tube was charged with alcohol/phenol and benzodioxinone at the ratios indicated in Table 1 and Table 2. The tube was sealed with a rubber septum, and freshly distilled CH_2Cl_2 (alcohol/phenol concentration: 0.25 M) was added under nitrogen. The nitrogen inlet was removed and the reaction vessel was sealed with parafilm. This reaction solution was then placed in a Rayonett RPR-100 reactor fitted with a test tube carousel and 300-nm bulbs and photolyzed for 4 h at 300 nm. The solution was then concentrated and purified by flash chromatography (silica gel, EtOAc/Hex).

Procedure B (Table 1, entry 4; Table 2, **15f** and **g**, **19a–d**, and **21a** and **b**): Same procedure as above but with degassed solvent. After photolysis, the crude reaction mixture was concentrated and redissolved in anhydrous methanol, then anhydrous K_2CO_3 (1.5 equiv) was added. After stirring for 0.5–2 h at RT, the mixture was poured into H_2O and extracted with EtOAc (3×). The organic phase was dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography (silica gel, EtOAc/Hex).

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[12] The reaction can be performed in several solvents with varying ratios of substrates. Optimal yields are obtained by irradiating a 1:2 or 2:1 mixture of reactants in benzene or CH_2Cl_2 at RT for 2–4 h. See Supporting Information for details.

[13] Formation of isocoumarin is a common problem associated with *ortho*-(2-oxo-alkyl)-substituted resorcinylates, requiring the use of masked ketones in synthetic sequences. For selected examples, see: a) R. M. Garbaccio, S. J. Stachel, D. K. Baeschlin, S. J. Danishefsky, *J. Am. Chem. Soc.* **2001**, *123*, 10903–10908; b) J. A. Elix, V. K. Jayanthi, *Aust. J. Chem.* **1987**, *40*, 1851–1859; c) J. A. Elix, J. H. Wardlaw, *Aust. J. Chem.* **1997**, *50*, 479–486.

[14] See the Supporting Information for UV/Vis absorbance spectra and the determination of relative quantum yields.

[15] Intermediates similar to **E** have been proposed previously during the photolysis of 3,1-benzoxathian-4-ones (A. O. Pedersen, S.-O. Lawesson, P. D. Klemmensen, J. Kolc, *Tetrahedron* **1970**, *26*, 1157–1161) and 2-phenyl-benzoxan-4-one (flavanone; P. O. L. Mack, J. T. Pinhey, *J. Chem. Soc. Chem. Commun.* **1972**, 451–452).

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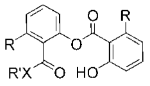
[17] They also explain a previous fruitless photolysis of a 2,2-dimethyl-substituted benzodioxinone, see reference [5].

[18] Y. Wu, X. Liao, R. Wang, X.-S. Xie, J. K. De Brabander, *J. Am. Chem. Soc.* **2002**, *124*, 3245–3253. In this study, we were forced to prepare a salicylate ester similar to **15g** through a Mitsunobu esterification reaction with an epimeric alcohol precursor as all attempts to prepare this compound by acylation failed.

[19] A similar observation was reported for acylations with acyclic α-oxoketenes: R. Shelkov, M. Nahmany, A. Melman, *J. Org. Chem.* **2002**, *67*, 8975–8982.

[20] In some cases, but more pronounced with aniline/amine substrates, further acylation of the phenol product leads to varying amounts (5–15%) of **F**. These can be converted into the desired salicylates **12**, **15f** and **g**, **19a–d**, and **21a** and **b** by treatment with K_2CO_3 in MeOH.



F: X = O, NR''

[21] For those cases examined, alternative procedures failed to deliver the corresponding esters/amides in yields higher than 0–36%. See Supporting Information for examples.