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Catalyst-free synthesis of 3,1-benzoxathiin-4-ones/1,3-benzodioxin-4-ones†

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An unambiguous and precise method for the synthesis of 3,1-benzoxathiin-4-ones/1,3-benzodioxin-4-ones by the reaction of propargylic alcohols and salicylic/thiosalicylic acids under a catalyst-free and open-air atmosphere is described. This strategy is found to be quite general using various 2-mercapto and 2-hydroxybenzoic acids providing benzoxathiinones/benzodioxinones in good yields.

Heterocycles form the largest classical division of organic chemistry and are of massive importance biologically and industrially. One of the striking structural features[1] inherent to heterocycles, which continue to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in a defined three-dimensional representation. Among them, sulfur- and oxygen-containing heterocyclic compounds have attracted the interest of researchers through decades of historical development of organic synthesis.[2] The relevance of heterocycles having oxygen and sulfur atoms comes from the significant changes in the cyclic molecular structure caused by the difference in the electronic configuration, unshared pair of electrons and ultimately the electronegativity between the heteroatom and carbon.[3]

3,1-Benzoxathiin-4-ones are typically derived from the reaction of 2-mercaptobenzoic acid and the significance of this class of molecules gets further impetus due to their involvement as intermediates in the synthesis of biologically active scaffolds. The synthesis and reactivity of benzoxathiin-4-ones have not been extensively studied so far as only a few reports are available for the synthesis of 3,1-benzoxathiin-4-ones.[4] Noticeably, 3,1-benzoxathiin-4-ones have been known as insecticides,[5a] crop protection agents[5b] and fungicides[5c] (Fig. 1).

However, benzo[*d*][1,3]dioxin-4-ones play an important role in natural products; maldoxin[6,7] and drug research; nucleoside base transporter inhibitors,[8] and antiplasmoidal and cytotoxicity[9] topoisomerase I inhibitors[10] (Fig. 1). These compounds act as potential intermediates and could be converted into flavones, aurones and phloroglucinols.[11] Benzodioxinones have been useful for the synthesis of chromones *via* nickel catalyzed cycloaddition with alkynes[12] and they act as photoinitiators for free radical polymerization[13] and undergo photolytic reactions with alcohols to form salicylate derivatives.[14] Natural products possessing a rare 1,3-benzodioxin-4-one

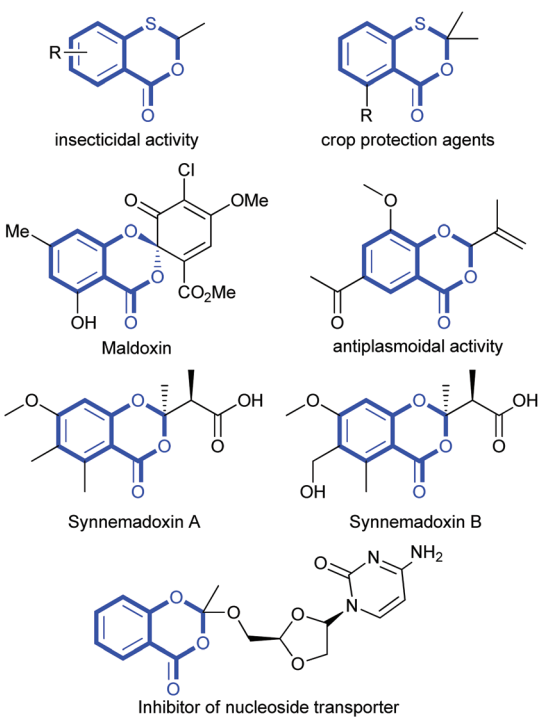

Fig. 1 Bioactive molecules possessing 3,1-benzoxathiin-4-ones/1,3-benzodioxin-4-ones.

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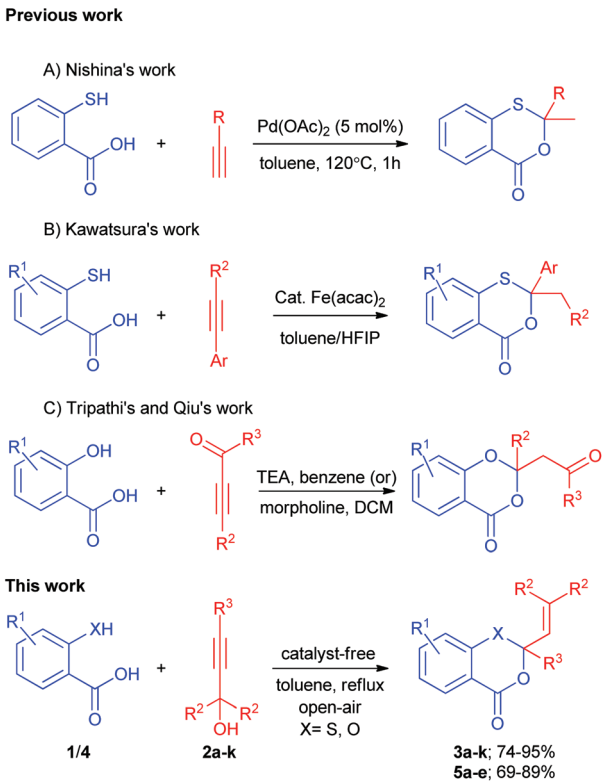
scaffold, synnemadoxins A & B (Fig. 1), were isolated from the *Synnemapestaloides* species and evaluated for their antimicrobial, antifungal and antibiotic activities.[15]

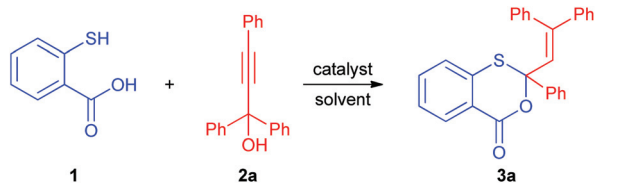
Nishina and co-workers developed[16] the synthesis of benzoxathiinones through regioselective hydrothiolation of alkynes with a palladium catalyst (Scheme 1). Kawatsura and co-workers demonstrated[17] the iron-catalyzed intermolecular coupling of alkynes with thiosalicylic acid for the synthesis of 3,1-benzoxathiinone derivatives through intermolecular hydrothiolation and sequential intramolecular cyclization. Both terminal and substituted ynones have been used to prepare 4*H*-benzo[*d*][1,3]dioxin-4-ones in the presence of a base, triethylamine[18] or morpholine.[19] The preparation of benzoxathiinones and benzodioxinones involving strong acidic/basic conditions, transition metal catalysts, toxic reagents, and high cost and also existing as intermediates in some cases have severe drawbacks for industrial applications. In continuation of our effort[20] to explore the chemistry of propargyl alcohols, we herein report a method for the synthesis of 3,1-benzoxathiin-4-ones/1,3-benzodioxin-4-ones from the reaction of propargylic alcohols and salicylic acids without any catalyst under open-air atmosphere.

Our initial investigation began with the examination of different catalysts and reaction conditions for the reaction of thiosalicylic acid **1** with propargylic alcohol **2a** (Table 1). A wide variety of transition metals promoted the hydrothiolation/intramolecular cyclization sequence. To achieve this, the



Scheme 1 Synthesis of 3,1-benzoxathiin-4-ones/1,3-benzodioxin-4-ones.

Table 1 Survey of reaction conditions for 3,1-benzoxathiin-4-ones (**3a**)[a,b]



Entry	Catalyst	Solvent	*T* (°C)	*t* (h)	Yield (%) **3a**[b]
1	$FeCl_3$	Toluene	Rt	12	45
2	$Cu(OAc)_2$	Toluene	Rt	12	40
3	$Pd(OAc)_2$	Toluene	Rt	12	78
4	$Pd(OAc)_2$	Toluene	Reflux	12	82
5	$Fe(acac)_2$	Toluene	Reflux	12	43
6	$Cu(acac)_2$	Toluene	Reflux	12	51
7	$AgNO_3$	Toluene	Reflux	12	61
8	$PdCl_2(PPh_3)_2$	Toluene	Reflux	24	52
9	$Pd(dba)_2$	Toluene	Reflux	16	46
10	$NiCl_2$	Toluene	Reflux	15	21
11	—	**Toluene**	**Reflux**	**12**	**86**
12	—	CH_2Cl_2	Reflux	12	Trace
13	—	1,4-Dioxane	Reflux	12	25
14	—	DMF	Reflux	12	31
15	—	Benzene	Reflux	12	48
16	—	H_2O	Reflux	12	nr[c]
17	—	C_6H_5F	Reflux	12	23
18	—	C_6H_5Cl	Reflux	12	51
19	—	*o*-Xylene	Reflux	12	41
20	—	*m*-Xylene	Reflux	12	46

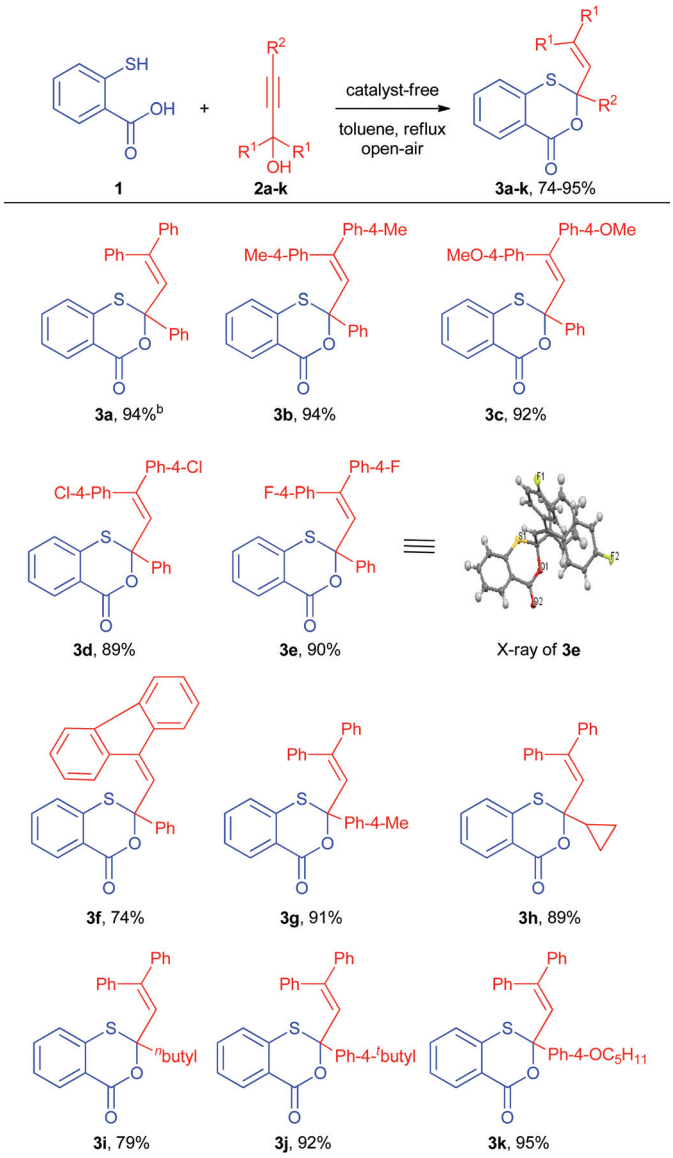
Entry 11 is the optimized best reaction conditions for this transformation. [a] Reaction conditions: Reaction of thiosalicylic acid **1** and propargylic alcohol **2a** was carried out in 10 mL of solvent under open-air atmosphere. [b] Yield of the isolated product after column chromatography. [c] nr = no reaction.

reaction of an equimolar amount of thiosalicylic acid **1**, propargylic alcohol **2a** and 5 mol% of $FeCl_3$ in toluene at room temperature for 12 h resulted in the formation of benzoxathiin-4-one **3a** in 45% isolated yield (Table 1, entry 1). The structure of compound **3a** was confirmed using IR, NMR and HRMS analyses. A low product yield was observed when the reaction was performed in the presence of $Cu(OAc)_2$ as a catalyst at room temperature (Table 1, entry 2). The reaction was repeated in toluene in the presence of 5 mol% $Pd(OAc)_2$ as a catalyst at room temperature to provide 78% yield of **3a** (Table 1, entry 3). The above reaction was performed under reflux conditions to obtain **3a** in 82% yield (Table 1, entry 4). Then, common metal catalysts, $Fe(acac)_2$, $Cu(acac)_2$, $AgNO_3$, $PdCl_2(PPh_3)_2$, $Pd(dpa)_2$ and $NiCl_2$, were also investigated with varying reaction times (Table 1, entries 5–10), but a low yield of product **3a** was obtained. On the other hand, the reaction was performed without adding a catalyst under reflux conditions for 12 h to afford **3a** in 86% yield (Table 1, entry 11). Besides, the screening of numerous solvents was incompatible for the synthesis of the desired product **3a** (Table 1, entries 12–20). Finally, the optimized reaction conditions were found to be as follows: no catalyst and use of toluene under reflux conditions under open-air atmosphere for the formation of **3a** (Table 1, entry 11).

With the optimized reaction conditions, we eventually tested the substrate array for the synthesis of 1,3-benzoxathiin-4-ones **3a–k** using thiosalicylic acid **1** and propargylic alcohols **2a–k** as illustrated in Table 2. Various propargylic alcohols reacted with thiosalicylic acid to give 3,1-benzoxathiin-4-ones **3a–k** in good yields. The electron-withdrawing and -donating groups present on the propargylic alcohol were well tolerated to afford the desired 3,1-benzoxathiin-4-ones **3b–e** in good yields. Fluorenyl propargylic alcohol also reacted efficiently to provide **3f**. The scope of R^2 as *p*-MeC_6H_4 in propargylic alcohol to provide **3g** in 91% yield was also determined. Furthermore, the scope of this reaction was tested with cyclopropyl and alkyl groups at the R^2 position of propargylic alcohol, and the needed product **3h** was formed in good yield. The alkyl substituent at the R^2 position in propargylic alcohol was also found to yield 79% of product **3i**. Furthermore, *t*-butyl and pentoxy phenyl substituted groups at the R^2 position of propargylic alcohols enabled excellent yields of 3,1-benzoxathiin-4-ones **3j–k**. The product **3e** was re-crystallized using hexane/EtOAc as colourless crystals and single-crystal X-ray analysis was performed[21] to unambiguously confirm the proposed structure and its solid-state structure shows C–H···O, C–H···F and C–H···π interactions. Regrettably, the desired product was not formed when using 2-mercaptonicotinic and 3-mercaptopicolinic acids and this may be due to the presence of tautomerism and the involvement of the pyridine ring during the course of the reaction.

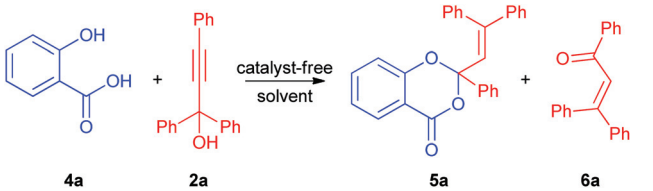
This protocol was further extended to salicylic acid **4a** with propargylic alcohol **2a** in a similar manner to yield product **5a** in 70% yield and product **6a** in 30% yield *via* a Meyer–Schuster rearrangement (Table 3, entry 1). This may be due to the lower nucleophilicity of oxygen in salicylic acid **4** than sulphur in thiosalicylic acid **1**. In order to avoid the byproduct **6a**, the screening of various solvents was performed but it was unsuited for this transformation (Table 3, entries 2–5). Furthermore, the flow rate of propargyl alcohol **2a** was controlled using a syringe pump, and it was helpful in minimizing the product **6a** *via* a Meyer–Schuster rearrangement (Table 3, entries 6–8). The addition of propargyl alcohol **2a** was carried out with a 0.2 mL h^{-1} flow rate using a syringe pump to provide more than 99% yield of product **5a** with a trace amount of **6a** based on HPLC (Table 3, entry 8). With the above information in hand, the optimized reaction conditions of 1,3-benzodioxinones were found to be the controlled addition (0.2 mL h^{-1}) of propargyl alcohol **2a** into salicylic acid

Table 2 Catalyst free synthesis of 3,1-benzoxathiin-4-ones (**3**)[a]



[a] Reaction conditions: Reactions of thiosalicylic acid **1** (1.0 equiv.) and propargylic alcohols **2a–k** (1.0 equiv.) were carried out in 10 ml of toluene under reflux conditions under open-air atmosphere for 12 h. [b] Yield of the isolated product after column chromatography.

Table 3 Survey of reaction conditions for 1,3-benzodioxin-4-ones (**5a**)[a]



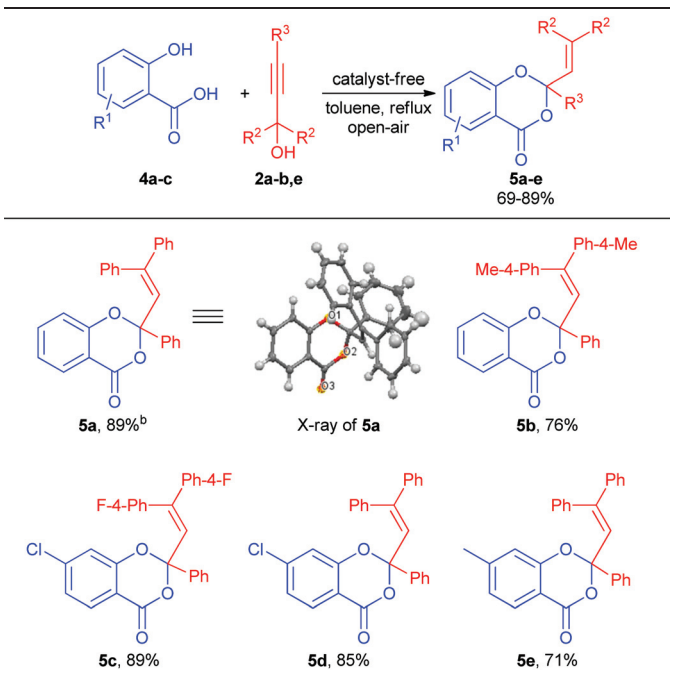
Entry	Solvent	Flow-rate of **2a** (mL h^{-1})	*t* (h)	Yield (%) **5a**/**6a** [b]
1	Toluene	—	12	70/30
2	*p*-Xylene	—	12	15/57
3	Benzene	—	12	—/69
4	DMF	—	12	nr[c]
5	DMSO	—	12	nr[c]
6	Toluene	1	5	92/8
7	Toluene	0.4	8	98/2
8	**Toluene**	**0.2**	**10**	**99/—**

Entry 8 is the optimized best reaction conditions for this transformation. [a] Reaction conditions: Reaction of equimolar amounts of salicylic acid **4a** and propargylic alcohol **2a** was carried out in 10 mL of solvent under reflux conditions under open-air atmosphere. [b] Yield of the product based on HPLC. [c] nr = no reaction.

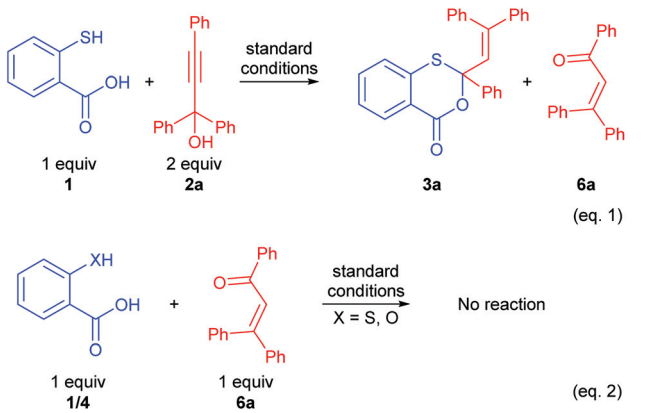
4a in the absence of any catalyst in toluene under reflux conditions under open-air atmosphere for the formation of **5a** (Table 3, entry 8). Furthermore, the scope of propargylic alcohols was tested using these optimized reaction conditions (Table 4). Reactions of propargylic alcohols bearing either electron-donating or -withdrawing groups were performed for this transformation to furnish products **5b–c**. Furthermore, the scope of salicylic acids for these reactions was examined. Chloro-substituted salicylic acid worked well compared to methyl-substituted salicylic acid with the reactions of propargylic alcohols under optimized conditions providing **5c–e** in good yields. The product **5a** was re-crystallized using hexane/EtOAc as colourless crystals and single-crystal X-ray analysis was carried out[21] to unambiguously confirm the proposed structure and its solid-state structure shows three C–H···O and two C–H···π interactions. Unfortunately, the reaction was not successful when tertiary propargylic alcohols having an unsymmetrical substituent, a heteroaryl substituent, terminal alkynes (R^2 = H) or alkyl substituents at R^1 and R^2 positions were used. Primary or secondary propargylic alcohols also failed to provide the desired product and it may be due to the lower stability of carbocation intermediates formed.

In order to gain insight into the reaction mechanism, a few control experiments (Scheme 2) were performed. The reaction of 1 equiv. of thiosalicylic acid **1** was carried out with 2 equiv. of propargylic alcohol **2a** to afford the corresponding 3,1-benzoxathiin-4-one **3a** (56% yield) with α,β-unsaturated carbonyl compound **6a** (41% yield) as a byproduct (eqn (1), Scheme 2).

Table 4 Catalyst free synthesis of 1,3-benzodioxin-4-ones (**5**)[a]



[a] Reaction conditions: Controlled addition (0.2 mL h^{-1}) of propargylic alcohols **2a**, **b**, and **e** (1.0 equiv.) into salicylic acids **4** (1.0 equiv.) in 10 ml of toluene at reflux conditions in an open-air atmosphere for 10 h. [b] Yield of the isolated product after column chromatography.

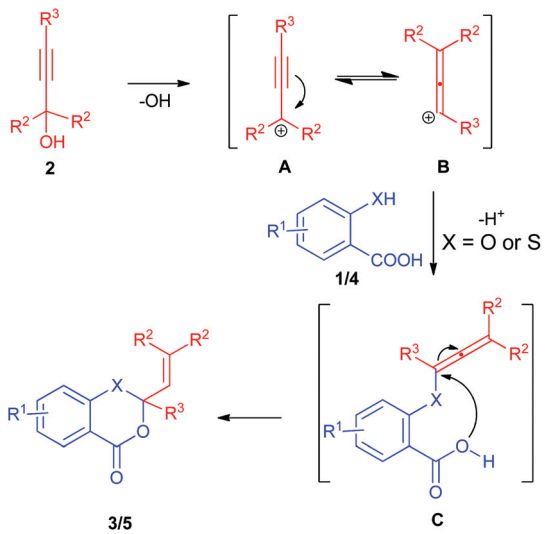


Scheme 2 Control experiments.

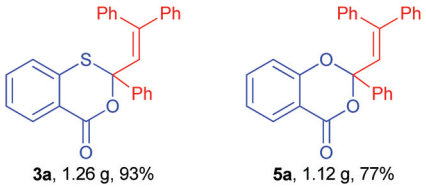
However, the reaction of an equimolar amount of acid **1/4** and α,β-unsaturated carbonyl compound **6a** under the optimized reaction conditions failed to give the desired products **3a**/**5a** (eqn (2), Scheme 2). Based on the above control experiments, it is concluded that the reaction does not proceed *via* the Meyer–Schuster rearrangement.

Based on the product structure, we propose a plausible mechanism for the formation of 3,1-benzoxathiin-4-ones **3**/1,3-benzodioxin-4-ones **5** (Scheme 3). The propargyl hydroxyl group of substrate **2** initially generated propargylic cation **A** under reflux conditions, which would undergo subsequent tautomerism to generate the allenic cation **B**. The intermolecular nucleophilic attack of the alcoholic group in acid **1**/**4** onto **B** affords intermediate **C** which on further cyclization provides product **3**/**5**.

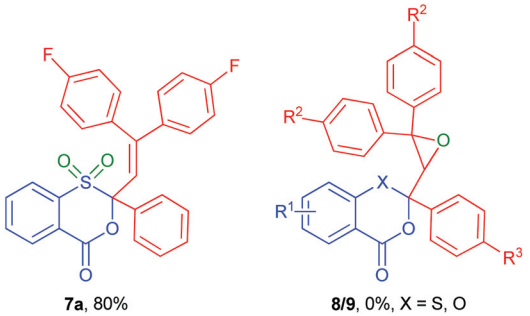
To demonstrate the consistency and practicality of the present synthetic methodology, gram-scale experiments using propargylic alcohol **2a** and acid **1**/**4a** were carried out to afford the corresponding products **3a**/**5a** in good yields (Scheme 4). It



Scheme 3 The plausible mechanism for the synthesis of 3,1-benzoxathiin-4-ones **3** and 1,3-benzodioxin-4-ones **5**.



Scheme 4 Gram scale preparation of 3,1-benzoxathiin-4-one **3a** and 1,3-benzodioxin-4-one **5a**.



Scheme 5 Synthetic utility of compounds.

is worth mentioning that thiosalicylic/salicylic acid could be easily handled as they are stable and show no changes of the product **3**/**5** under open air over a period of a month at room temperature.

For synthetic use, 3,1-benzoxathiin-4-one **3e** was reacted with *m*-CPBA to afford sulfone **7a** in 80% yield (Scheme 5). The possible formation of epoxide **8**/**9** by the reaction of **3**/**5** with *m*-CPBA was not achieved even after 24 h.

Conclusion

In summary, the development of a catalyst-free method for the synthesis of 3,1-benzoxathiin-4-ones/1,3-benzodioxin-4-ones is described. Studies of salicylic acids and propargylic alcohols have contributed to this reaction providing an array of benzoxathiine-4-ones/benzodioxin-4-ones in an easy manner. The ready availability of substrates, broad scope and operational simplicity of this process are beneficial for its large-scale application. A study on the development of the related molecules is currently ongoing in our laboratory.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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21 CCDC 2044132 (**3e**) and 2044131 (**5a**)† contain the supplementary crystallographic data for this paper.