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Stereoselective Synthesis of Functionalized Benzooxazepino[5,4-*a*]isoindolone Derivatives via Cesium Carbonate Catalyzed Formal [5 + 2] Annulation of 2-(2-Hydroxyphenyl)isoindoline-1,3-dione with Allenoates

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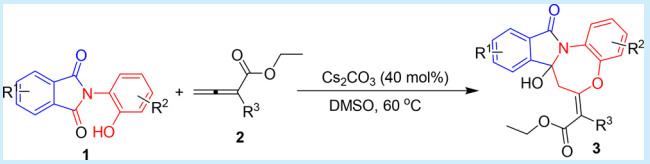
Supporting Information

ABSTRACT: In this work, we present a strategy for the stereoselective synthesis of functionalized benzooxazepino[5,4-*a*]isoindolone derivatives via a Cs_2CO_3-catalyzed domino β-addition and γ-aldol reaction of 2-(2-hydroxyphenyl)-isoindoline-1,3-dione derivatives with allenoates, which offers an avenue for a combination of the structural unity between benzooxazepine and isoindolone motifs in synthetically useful yields with high stereoselectivities under mild conditions. Remarkably, it is the first example of highly stereoselective Cs_2CO_3-catalyzed formal [5 + 2] annulation of 2-(2-hydroxyphenyl)isoindoline-1,3-dione with allenoates.



It is highly of interest to effectively construct diverse heterocyclic molecules based on privileged scaffolds from the viewpoints of synthetic chemistry and drug discovery.[1] Benzooxazepine[2] and isoindolone moieties[3] are both among important privileged ring systems because their derivatives are valuable backbones for the discovery of new biologically active molecules or therapeutic agents. Therefore, the chemical entry, benzooxazepino[5,4-*a*]isoindolone, with a combination of the structural unity between benzooxazepine and isoindolone motifs may exhibit different biological characteristics in drug discovery (Figure 1). However, the methods for the synthesis

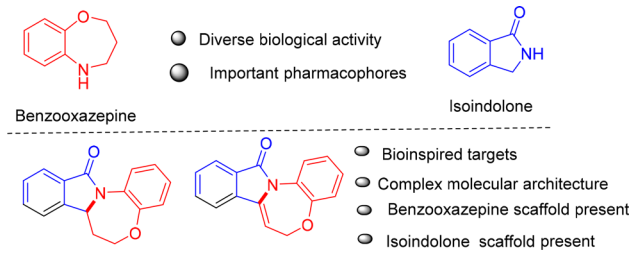


Figure 1. Backbones of benzooxazepine and isoindolone moieties.

of these compounds are very scarce despite their potential applications in medicinal chemistry. Accordingly, searching for an efficient route to synthesize benzooxazepino[5,4-*a*]-isoindolones would offer more promising candidates for biological screening in a way that was neither possible nor required before.

Allenoates have been proven to be an important class of substrates to construct various important heterocyclic compounds with various reaction partners,[4] such as imines,[5] aldehydes,[6] ketones,[7] α, β-unsaturated carbonyl compounds,[8] and azomethine imines,[9] in the presence of various base or acid catalysts. Among them, carbonate is a kind of readily available commercial and safe normal inorganic base, and it is also used as a catalyst in these reactions. Shi and co-workers first reported carbonate-catalyzed reactions of ethyl allenoate with salicylic aldehydes to access the functionalized chromenes in good yields (Figure 2).[10] Then Philipp Selig and co-workers reported a graceful method for the synthesis of 2,3-disubstituted quinolines via carbonate-catalyzed reaction of allenoates with *N*-protected *o*-aminobenzaldehydes.[11] Recently, phthalimide derivatives have been disclosed as good reaction partners with

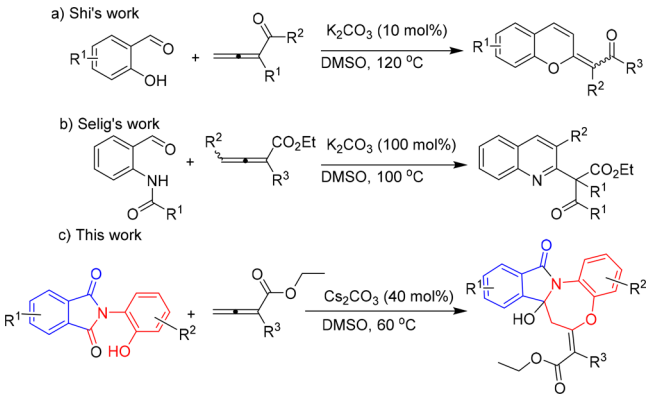


Figure 2. Examples for the reactions of allenoates with carbonyl electrophiles.

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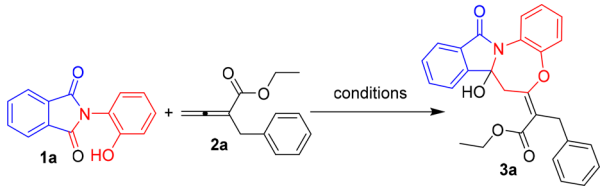
allenoates[12] or activated alkynes[13] under various base catalysis conditions. However, a cesium carbonate catalyzed reaction of allenoates with phthalimide derivatives has never been reported. Herein, we describe the first cesium carbonate catalyzed domino β-addition and γ-aldol reaction of allenoates to 2-(2-hydroxyphenyl)isoindoline-1,3-dione for the stereoselective construction of highly functionalized benzooxazepino[5,4-*a*]isoindolone deravatives. At the outset of our study, 2-(2-hydroxyphenyl)isoindoline-1,3-dione **1a** and allenoate **2a** were selected for the initial reaction in the presence of 20 mol % PPh_3 in DMF at 40 °C (Table 1, entry 1). No target product **3a**

Table 1. Survey on Conditions for Formation of 3a[a]



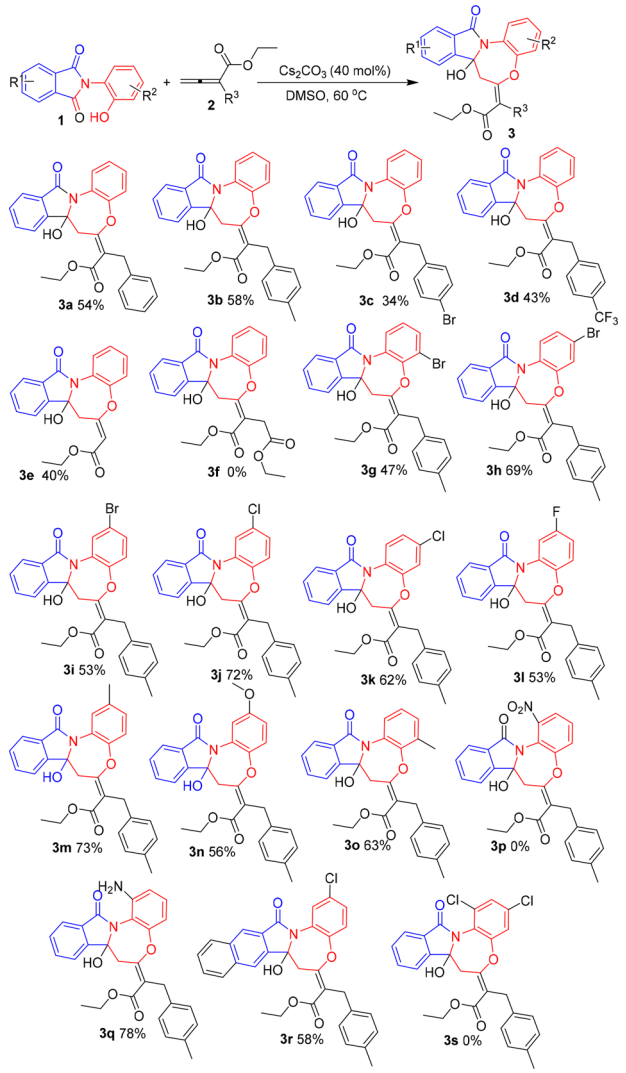
entry	catalyst	solvent	T [°C]	t [h]	yield [%][b]
1	Ph_3P (20 mol %)	DMF	40	48	0
2	Bu_3P (20 mol %)	DMF	40	48	0
3	Et_3N (20 mol %)	DMF	40	48	0
4	Na_2CO_3 (20 mol %)	DMF	40	48	trace
5	K_2CO_3 (20 mol %)	DMF	40	48	trace
6	Cs_2CO_3 (20 mol %)	DMF	40	48	trace
7	NaOH (20 mol %)	DMF	40	48	trace
8	Na_2CO_3 (20 mol %)	DMF	60	9	15
9	K_2CO_3 (20 mol %)	DMF	60	9	17
10	Cs_2CO_3 (20 mol %)	DMF	60	10	22
11	NaOH (20 mol %)	DMF	60	6	5
12	Cs_2CO_3 (20 mol %)	DMSO	60	12	52
13	Cs_2CO_3 (20 mol %)	ethanol	60	48	0
14	Cs_2CO_3 (20 mol %)	H_2O	60	48	0
15	Cs_2CO_3 (20 mol %)	DCM	60	48	0
16	Cs_2CO_3 (20 mol %)	THF	60	48	0
17	Cs_2CO_3 (20 mol %)	toluene	60	48	0
18	Cs_2CO_3 (20 mol %)	DMSO	40	20	49
19	Cs_2CO_3 (20 mol %)	DMSO	100	1	0
20	Cs_2CO_3 (0 mol %)	DMSO	60	48	0
21	Cs_2CO_3 (40 mol %)	DMSO	60	3	54
22	Cs_2CO_3 (100 mol %)	DMSO	60	1	0

[a]To a mixture of **1a** (0.15 mmol) and **2a** (0.1 mmol) in anhydrous DMSO (1.0 mL), Cs_2CO_3 (0.04 mmol, 14 mg) was added. The resulting solution was stirred at 60 °C. [b]Isolated yield based on **2a**.

was formed. Then Bu_3P with relatively stronger nucleophilicity and Et_3N were also tested in the reaction, and they did not afford any good signs of formation of product **3a**. However, product **3a** was found with a negligible yield when an inorganic base, such as Na_2CO_3, K_2CO_3, Cs_2CO_3, and NaOH, was used as a reaction promoter. Gratifyingly, a moderate yield of **3a** was given using Cs_2CO_3 as the catalyst when the reaction was heating at 60 °C in DMF (entry 10). Encouraged by this result, various solvents were then evaluated to optimize the reaction conditions. Most of them proved to be unusable for the formation of **3a**, such as ethanol, toluene, H_2O, THF, and DCM, and only DMSO gave the best result for **3a** (entries 12−17). Further examination showed that the temperature and the amount of catalyst are crucial for the formation of **3a**. Thus, we established the optimal reaction conditions for the construction of benzooxazepino[5,4-*a*]isoindolone deravatives as follows: use of 40 mol % Cs_2CO_3 as the catalyst and DMSO as the solvent to perform the reaction at 60 °C.

With the optimized reaction conditions in hand, the generality and efficiency of different allenoates were examined for this transformation (Scheme 1). Overall, the desired

Scheme 1. Synthesis of Benzooxazepino[5,4-*a*]isoindolones[a,b]



[a]To a mixture of **1** (0.15 mmol) and **2** (0.1 mmol) in anhydrous DMSO (1.0 mL), Cs_2CO_3 (0.04 mmol, 14 mg) was added. The resulting solution was stirred at 60 °C. [b]Isolated yield based on **2**.

products were formed in all the reactions of 2-(2-hydroxyphenyl)isoindoline-1,3-dione **1a** with different α-benzyl substituted allenoates in moderate to good yields. The nature of the substituent on the benzene ring of the α-benzyl substituted allenoates had a slight impact on the yields. To our delight, α-unsubstituted allenoate also reacted smoothly with **1a** to give the desired benzooxazepino[5,4-*a*]isoindolone derivative in a moderate yield. However, α-ethoxycarbonylmethyl substituted allenoate did not generate the target product. Ethyl 2-methylbuta-2,3-dienoate and ethyl penta-2,3-dienoate were also checked; however, they also did not give the target products. Many 2-(2-hydroxyphenyl)isoindoline-1,3-diones

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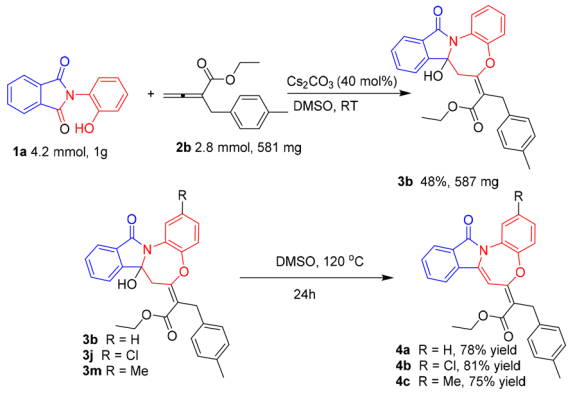
were then synthesized and examined in this transformation coupling with α-benzyl substituted allenoate. The results indicate that various substituted phenyl moieties, possessing electron-donating or weak electron-withdrawing substituents (F, Cl, Br), were well tolerated in this transformation. However, for a substrate with a strong electron-withdrawing substituent (NO_2) attached on the benzene ring, no product was found. It is worth mentioning here that, under the above conditions, the substrate with a free anmino group could react with allenoate to furnish the corresponding benzooxazepino[5,4-*a*]isoindolone derivative **3q** in a yield of 78%. The reaction was also effective at producing the corresponding product in moderate yield when the substrate with a large aromatic ring (naphthyl group) instead of benzene was present. When double chlorine was used as a substituent, the reaction did not proceed.

To demonstrate the synthetic potential of this catalytic system, the gram-scale preparation of **3b** was investigated. The reaction of 4.2 mmol of the starting material (**1a**) proceeded smoothly, delivering the corresponding product **3b** in 48% yield without a significant loss of efficiency (small scale, 58%). The synthetic application of this methodology was demonstrated by the reaction of **3**. The dehydration products **4** were obtained in good yields when various hydroxybenzooxazepino[5,4-*a*]-isoindolones **3** were exposed at 120 °C in DMSO for 24 h (Scheme 2).

Scheme 2. Gram-Scale and Synthetic Transformations



The structures of the products were undeniably confirmed by X-ray crystallographic analysis of compound **4a**. The ORTEP diagram of **4a** is shown in Figure 3.

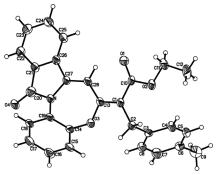


Figure 3. X-ray crystallographic analysis of **4a**.

On the basis of our experimental observations and known literature,[10] a plausible mechanism for the reaction is shown in Figure 4. Initially the non-nucleophilic base cesium carbonate deprotonates **1a** to generate intermediate **I**. The intermediate **I** then undergoes Michael addition to allenoate to give intermediate **II**, and the alternative resonance form **III** might then undergo intramolecular nucleophilic attack to form

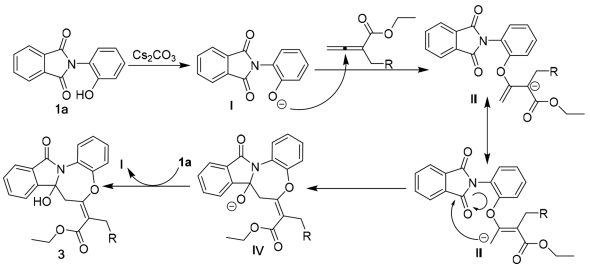


Figure 4. A plausible reaction mechanism for the formation of the reaction.

intermediate **IV**, followed by proton transfer to produce the desired product **3**.

In conclusion, an unprecedented steroselective Cs_2CO_3-catalyzed domino β-addition and γ-aldol reaction of 2-(2-hydroxyphenyl)isoindoline-1,3-dione derivatives with allenoates has been developed. This novel process, carried out under extremely mild conditions, provides access to functionalized benzooxazepino[5,4-*a*]isoindolone deravatives. Remarkably, the structures of these products may be attractive for potential drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00382.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra and high-resolution mass spectrometry (PDF)

Accession Codes

CCDC 1821747 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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