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Graphical Abstract

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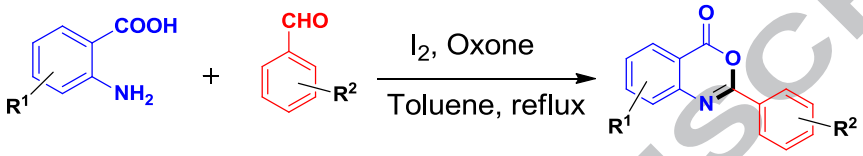

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Direct oxidative cascade cyclisation of 2-aminobenzoic acid and arylaldehydes to aryl 4H-3,1-benzoxazin-4-ones with oxone

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ABSTRACT

This paper presents a methodology of oxidative cascade cyclisation of 2-aminobenzoic acids and arylaldehyde using I_2 as a catalyst and an environmentally benign oxidant oxone. This method displays facile access to a diverse range of substituted aryl 4H-3,1-benzoxazin-4-ones. This synthetic methodology has many advantages such as: (1) easy availability of starting material, (2) transition metal- free condition (3) use of an environmentally benign oxidant.

1. Introduction

Synthesis of fused heterocycles is of particular interest to organic chemists because of its potential biological activity. Among them, 4H-3,1-benzoxazin-4-one derivatives are important skeletons due to their proven pharmaceutical activity[1]. For example, some of the drugs which contain 4H-3,1-benzoxazin-4-one as the core structure act as HSV-1 protease inhibitors[1a], human leukocyteelastase inhibitors[1b], chymotrypsin inactivator[1c], cathepsin G inhibitor[1d], serine protease inhibitor[1e] and humanchymase inhibitor[1f]. Moreover, some of the 4H-3,1-benzoxazin-4-one derivatives have been reported to have the ability to lower the plasma cholesterol. 4H-3,1-benzoxazin-4-ones also act as successful precursors for the biologically much important derivatives, such as quinazolin-4(3H)-ones and quinolin-2(1H)-ones[2]. Hence, it is no surprise that the synthesis of benzoxazinones has received intensive attention over the past decade.

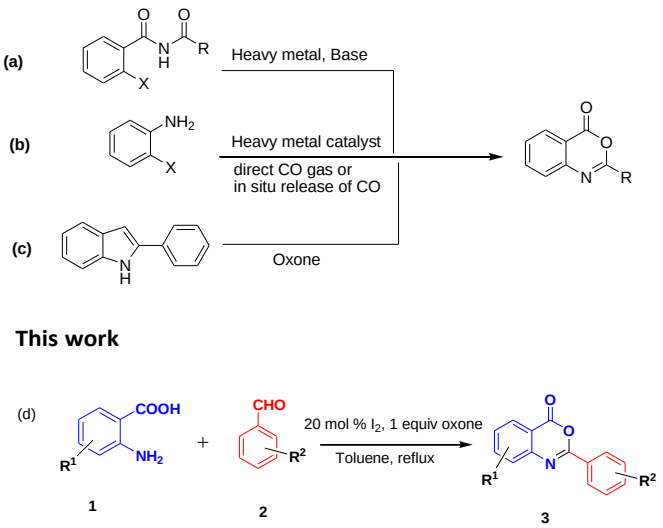
The most common methods for the synthesis of benzoxazinones are cyclisation of anthranilic acid with benzoyl chloride, cyclisation of N-acylanthranilic acid, ring transformation of isatoic anhydride and cyclisation of N-acylanthranilic acid under the influence of cyclization agent, cyanuric chloride[3]. In the last decade, other notable methods have been developed for the synthesis of benzoxazinones in order to improve the yield and reduce the cost of the reaction. These methods include copper(I) catalyzed cyclisation of N-acyl-2-iodobenzamide[4], oxidation of 2-arylindoles using oxone as the sole oxidizing agnent[5], intramolecular C−N coupling and rearrangement of N-acyl-2-halobenzamides using CuI as a catalyst[6], Ugi-type reaction of 1,1-dimethylethyl 2-isocyanobenzoates with N,N-dialkyliminium iodides[7]. In the last few years research for the synthesis of benzoxazinones has involved carbonyl insertion method using carbon monoxide (CO) using either carbon monoxide gas or in situ release of CO to avoid handling the gas. Palladium catalyzed carbonyl insertion method with CO gas with different starting materials was a highly reported method in the last decade[8]. In the case of carbonyl insertion using in situ prepared CO for the synthesis of benzoxazinones, Wu et al. have reported the synthesis of benzoxazinones from N-(*o*-bromoaryl)amides by palladium-catalyzed carbonylation with paraformaldehyde as the carbonyl source[9]. Manabe et al. have developed palladium catalyzed carbonylative synthesis form haloarenes with phenyl formate as the carbonyl source[10]. Recently, Ulven et al. have reported an interesting synthetic method for the synthesis of benzoxazinones from 2-iodobenzamide with oxalyl chloride as the carbonyl source[11]. Though the successful synthesis of benzoxazinones from these methods is possible, the method which is highly desirable and compatible under all conditions is one that utilizes a simple starting material and proceeds under mild reaction condition. In continuation of our research on the synthesis of benzoxazinones[12], we report a simple, efficient and economical synthesis of 2-arylbenzoxazinones from anthranilic acid and benzaldehyde with oxone as the sole oxidizing agent.

2. Results and Discussion

We began the study of the synthesis of 2-arylbenzoxazinones reaction utilizing 2-aminobenzoic acid **(1a)** and benzaldehyde **(2a)** to optimize the reaction condition such as oxidants, catalysts and solvents. When the reaction was carried out in DMF solvent

in the presence of 20 mol% of iodine (catalyst) and one equivalent of oxone (oxidant) for 4 h at reflux condition, the

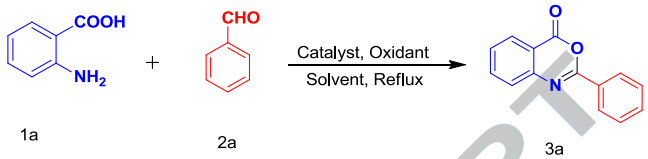
Scheme 1 Previous reported strategies for the synthesis of 2-arylbenzoxazinones.



desired product 2-phenyl-4H-benzo[d][1,3]oxazin-4-one was obtained in 30 % yield (Table 1, entry 13). With this initial achievement, various solvents have been examined for this cascade reaction in order to improve the yield. Toluene was found to be the most suitable solvent for this reaction to give **3a** with 83 % yield (Table 1, entry 1). We obtained only inferior results when we used other solvents such as polar protic solvents and nonpolar solvents (Table 1, entries 12-17). Solvent optimization was carried out under the reflux condition of the reaction. The effect of various oxidants for this cascade reaction was examined. A study of the screening of oxidants such as O_2, H_2O_2, DDQ, CrO_3, *m*-CPBA, $Na_2S_2O_8$ and oxone revealed that the best choice of oxidant is oxone (Table 1, entry 1). Subsequently, the effect of Lewis acid for this cascade reaction was carried out. Among the tested Lewis acids such as I_2, $AlCl_3$, $FeCl_3$, $SnCl_2$, and $ZnCl_2$, I_2 afforded the **3a** in the highest yield (Table 1, entries 1-5) when used in 10 mol% catalyst load. Moderate yield was obtained in the presence of $AlCl_3$ and $FeCl_3$ while in other cases the reaction did not proceed at all. Other Bronsted acids such as acetic acid and *p*-toluenesulfonic acid did not yield the product at all. When I_2 load was increased to 30 mol %, no positive result was observed and the yield was the same as that of 20 mol%. Using 10 mol% of I_2 eventually decreased the product yield. Further increase in the catalyst did not give any improvement in the yield. On the basis of reaction condition optimization results, 20 mol% I_2 and one equivalent oxone in toluene solvent at reflux condition was used for further investigation.

With optimized reaction condition in hand, the substrate scope of this oxidative cascade reaction was investigated. As shown in the table 2, a series of aromatic aldehydes **2** was allowed to react with 2-aminobenzoic acid under the reaction condition developed. Arylaldehyde derivatives with both electron donating (4-ethyl, 4-Br), neutral and electron withdrawing (4-F) groups on the aromatic ring participated in this reaction smoothly with average to good yield of **3.** In addition to this, 2-chlorobenzaldehyde gave the corresponding product with the yield of 77 % (Table 2, 3b), which indicates that steric effects had little influence on this reaction since 2-chlorobenzaldehyde gave comparable yield as that of 4-chlorobenzaldehyde (Table 2, 3d). This I_2 catalysed, oxidative cascade reaction could tolerate many functional groups such as C-Cl bond, C-Br bond, NO_2 group in aryl aldehydes. We have tried the same reaction in alkyl aldehyde but we could not get the desired product.

Table 1 Optimization of reaction conditions[a]



entry	Catalyst	Oxidant	Solvent	Yield (%)[a,b]
1	I_2	Oxone	PhMe	83
2	$AlCl_3$	Oxone	PhMe	54
3	$FeCl_3$	Oxone	PhMe	62
4	$SnCl_2$	Oxone	PhMe	---
5	$ZnCl_2$	Oxone	PhMe	---
6	I_2	O_2	PhMe	17
7	I_2	H_2O_2	PhMe	27
8	I_2	DDQ	PhMe	32
9	I_2	CrO_3	PhMe	---
10	I_2	mCPBA	PhMe	12
11	I_2	$Na_2S_2O_8$	PhMe	---
12	I_2	Oxone	DMSO	72
13	I_2	Oxone	DMF	30
14	I_2	Oxone	Acetonitrile	26
15	I_2	Oxone	THF	21
16	I_2	Oxone	ETOH	16
17	I_2	Oxone	H_2O	---

[a]Unless otherwise noted, the reactions were carried out with 2 mmol of 1a and 2 mmol of 2a, 0.4 mmol of catalyst, and 2 mmol of oxidant in solvents under reflux condition.
[b]Isolated yield.

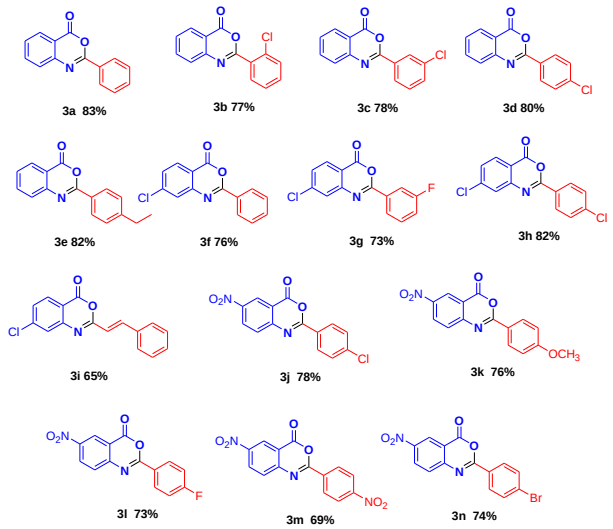


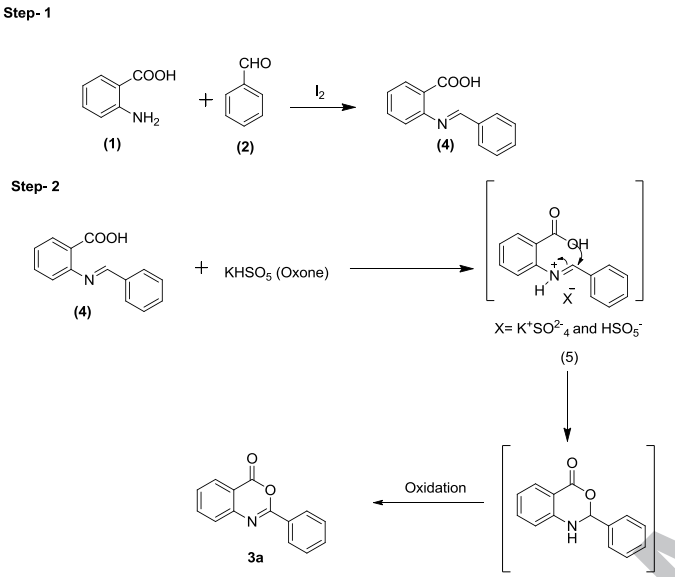
Table 2 Scope of arylaldehydes[a]

[a]Reaction conditions: Unless otherwise noted, the reactions were carried out with 2 mmol of 1 and 2 mmol of 2, 0.4 mmol of catalyst, and 2 mmol of oxone with toluene solvent under reflux condition. The samples were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported methods.

Considering the phenomenon, the following mechanism for the oxidative cascade reaction for the synthesis of 2-arylbenzoxazinones using 2-aminobenzoic acid and

benzaldehyde is proposed as example (Scheme 2). The first step is the formation of imine **4** from reaction between 2-aminobenzoic acid and benzaldehyde catalyzed by iodine. The second step involves the activation of imine group to iminium salt (5) by the active constituent $KHSO_5$ of oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)[13]. Subsequent cyclisation[3i] followed by oxidation leads to 2-arylbenzoxazinones.

Scheme 2 Proposed reaction mechanism



3. Conclusion

In summary, we have developed I_2 catalysed oxidative cyclisation method for the synthesis of 2-arylbenzoxazinones using 2-aminobenzoic acid and arylaldehyde with oxone as oxidant. Such a novel, transition-metal-free simple reaction condition using inexpensive and readily available reagents, provides a convenient and highly efficient access to 2-arylbenzoxazinones. This synthetic protocol can tolerate a broad range of functional groups. In addition to this, precursor preparation from starting materials was not required in this reaction, which avoided multiple reaction steps.

4. Acknowledgment

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5. Experimental data

General procedure for the synthesis of 2-phenyl-4H-benzo[d][1,3]oxazine-4-one:

An oven dried three neck RB was loaded with 2-aminobenzoic acid (1) (2 mmol), benzaldehyde (2) (2 mmol), I_2 (0.4 mmol, catalyst) and oxone (1 equivalent, oxidant) in toluene (5 ml). Then, the reaction mixture was allowed to reflux for 4h. The completion of the reaction was monitored by TLC. After being cooled at room temperature the reaction mixture was poured in the saturated solution of sodium thiosulfate in order to remove iodine and extracted with ethylacetate. The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography (hexane(80)/ ethyl acetate (20)) on silica gel to afford 2-phenyl-4H-benzo[d][1,3]oxazine-4-one.

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Highlights

- Cascade cyclisation of 2-aminobenzoic acids and arylaldehyde using I_2 and oxone.
- Easy availability of starting material
- As many aromatic aldehydes are available reagents, the versatility of the product can be increased.
- Transition metal- free condition.
- Use of an environmentally benign oxidant.