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ARTICLE

Synthesis of Aryl 4*H*-3,1-benzoxazin-4-ones from 2-Aminobenzoic Acid and Arylaldehydes Using PEG-400 as an Efficient and Recyclable Reaction Medium

Dharmasothu Veeranna✉

ABSTRACT

Polyethylene glycol (PEG-400) has been discovered to be an effective eco-friendly solvent cum activator for the one-pot cyclization of 2-aminobenzoic acid and arylaldehyde. This method displays facile access to a diverse range of substituted aryl 4*H*-3,1-benzoxazin-4-onesThe reaction was performed under mild conditions and the generality of the one-pot reaction was investigated.

KEYWORDS

Oxidative cascade cyclization, 2-Aminobenzoic acid, Arylaldehyde, Polyethylene glycol, Catalyst-free conditions.

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INTRODUCTION

Green chemistry relates to the design of a process that minimizes the use and generation of hazardous substances. Green catalysis is one of the key areas of green chemistry. In the past decade, the use of alternative solvents such as ionic liquids, polyethylene glycol and super critical fluids has gained importance as green reaction media in view of environmental perception [1]. In this context, polyethylene glycol (PEG) has become an alternative reaction media to perform organic synthesis due to its inherent advantages over toxic solvents. Furthermore, PEG has emerged as a powerful phase transfer catalyst and performs many useful organic transformations under mild reaction conditions. In addition, PEG is inexpensive, easy to handle, thermally stable, non-toxic and recyclable. In this perspective, PEG as a solvent has been played a key role in the practice of green chemistry [2]. Synthesis of fused heterocycles is of particular interest to organic chemists because of its potential biological activity. Among them, 4*H*-3,1-benzoxazin-4-one derivatives are important skeletons due to their proven pharmaceutical activity [3].

Various methods of their synthesis have been reported in the literature. However, the most common methods for the synthesis of benzoxazinones are cyclization of anthranilic acid with benzoyl chloride, cyclization of N-acylanthranilic acid, ring transformation of isatonic anhydride and cyclization of N-acylanthranilic acid under the influence of cyclization agent, cyanuric chloride [4]. In the last decade, other notable methods

Author affiliations:

Department of Chemistry, S.R. & B.G.N.R. Government College (Autonomous), Khammam-507 002, India

✉To whom correspondence to be addressed:

E-mail: dsveeranna@gmail.com

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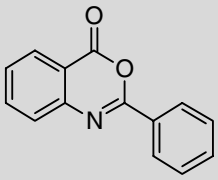
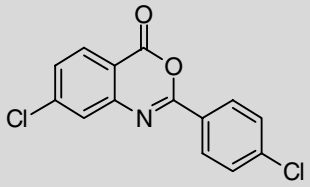
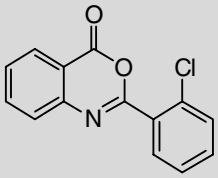
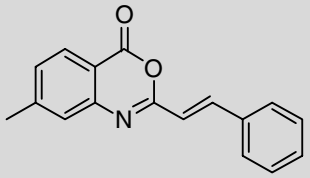
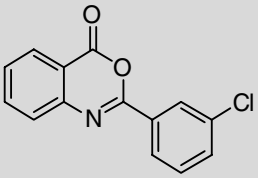
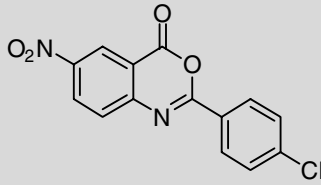
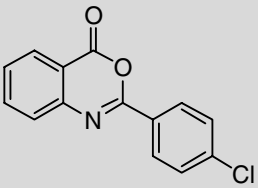
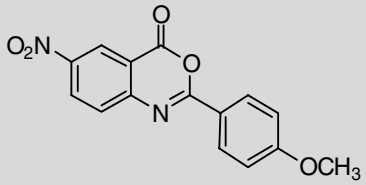
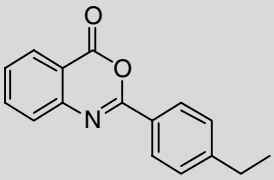
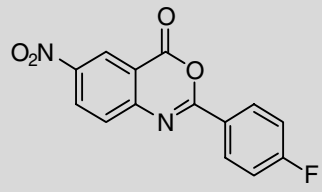
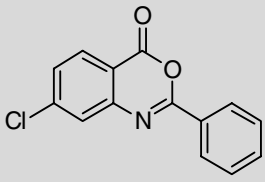
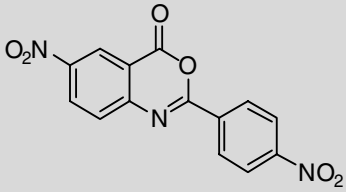
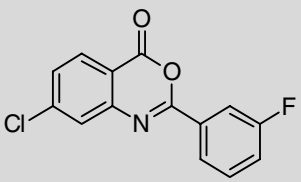
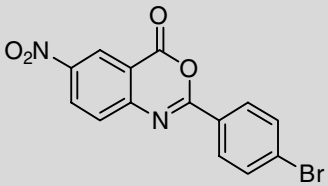
have been developed for the synthesis of benzoxazinones in order to improve the yield and reduce the cost of the reaction. These methods include copper(I) catalyzed cyclization of *N*-acyl-2-iodobenzamide [5], oxidation of 2-arylindoles using oxone as the sole oxidizing agnent [6], intramolecular CAN coupling and rearrangement of *N*-acyl-2-halobenzamides using CuI as a catalyst [7], Ugi-type reaction of 1,1-dimethylethyl 2-isocyanobenzoates with N,N-dialkyliminium iodides [8]. 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 [9]. In the case of carbonyl insertion using *in situ* prepared CO for the synthesis of benzoxazinones, Wu *et al.* [9] have reported the synthesis of benzoxazinones from N-(*o*-bromoaryl) amides by palladium-catalyzed carbonylation with *para*-formaldehyde as the carbonyl source. Manabe *et al.* [10] have developed palladium catalyzed carbonylative synthesis form haloarenes with phenyl formate as the carbonyl source. Recently, Ulven and Hansen [11] have reported an interesting synthetic method

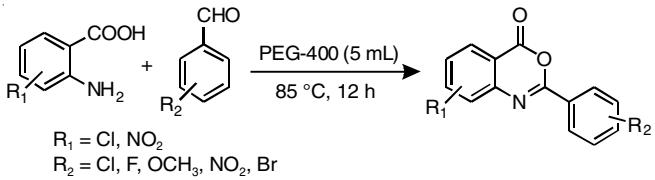
TABLE-1
PEG MEDIATED SYNTHESIS OF ARYL 4*H*-3,1-BENZOXAZIN-4-ONES

Compd.	Structure	Yield (%)*	Compd.	Structure	Yield (%)*
3a		85	**3h**		82
3b		75	**3i**		65
3c		77	**3j**		77
3d		80	**3k**		75
3e		82	**3l**		75
3f		75	**3m**		70
3g		73	**3n**		75

Reactions conditions: PEG-400 mediated synthesis of aryl 4*H*-3,1-benzoxazin-4-ones, *via* the condensation of 2-aminobenzoicacid with aldehydes. Unless otherwise specified, the reaction was carried out with **1** (2 mmol), **2a-o** (2 mmol) and PEG-400 (5 mL).
*Isolated yields of the products **3a-n** after column chromatography.

for the synthesis of benzoxazinones from 2-iodobenzamide with oxalyl chloride as the carbonyl source. 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 On the other hand, organic reactions in water without using harmful organic solvents is one of the current focuses today, especially in our current environmentally conscious society, because water is abundant, non-toxic and environmentally-friendly when compared with the traditionally used organic solvents. As we all know, poly-(ethylene glycol) (PEG) is a thermally stable, inexpensive, recoverable and non-toxic hydrophilic polymer. Meanwhile, the high solubility of PEGs in water and several organic solvents including alcohol and acetone [12,13] instead of their insolubility in less polar solvents such as hexane makes them easy to recover and high performance solvents for organic reactions [14,15].

In recent years, polyethylene glycol (PEG) has emerged as a powerful phase-transfer catalyst and performs many useful organic transformations under mild reaction conditions. Moreover, PEG is an inexpensive, easy to handle, thermally stable, non-toxic and recyclable in various organic transformations [2]. We report herein the first synthesis of 2-aminobenzoic acid arylaldehydes using PEG-400 as a recyclable medium without additional organic solvent and catalyst (**Scheme-I**).



Scheme-I: PEG mediated synthesis of aryl 4*H*-3,1-benzoxazin-4-ones

EXPERIMENTAL

General procedure for synthesis of aryl 4*H*-3,1-benzoxazin-4-ones by using PEG as a reaction medium: A mixture of the requisite aldehyde (2 mmol), 2-aminobenzoic acid (2 mmol) was taken in PEG (5 mL) and stirred at 85 °C for the appropriate time. After completion of the reaction, as monitored by TLC, the reaction mixture was poured into H_2O and extracted with EtOAc. The organic layer was removed under reduced pressure and the crude product was purified by column chromatography. The recovered PEG could be reused for a number of cycles without significant loss of activity.

RESULTS AND DISCUSSION

With optimized reaction condition in hand, the substrate scope of this oxidative cascade reaction was investigated. 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-1), which indicates that steric effects had little influence on this reaction since 2-chlorobenzaldehyde gave comparable yield as that of 4-chlorobenzaldehyde.

To the best of our knowledge there are no previous reports for the synthesis of aryl 4*H*-3,1-benzoxazin-4-onesderivatives by using PEG-400 as a reaction medium under catalyst-free conditions. The generality of this reaction was investigated for the synthesis of various aryl 4*H*-3,1-benzoxazin-4-ones derivatives by using a variety of aldehyde and 2-aminobenzoic acid (Table-1). In general, all the reactions were very clean and the aryl 4*H*-3,1-benzoxazin-4-onesderivatives were obtained in high yields. Aldehyde bearing electron-donating groups (Me) reacted efficiently; whereas in the presence of electron-withdrawing groups (NO_2) a slight decrease in the yield of the aryl 4*H*-3,1-benzoxazin-4-oneswas observed. The structures of all the products were determined from their analytical and spectroscopic (IR, ^{1}H NMR and ^{13}C NMR) data and by direct comparison with authentic samples [16].

Conclusion

In conclusion, we have developed an efficient and facile method for the synthesis of aryl 4*H*-3,1-benzoxazin-4-ones derivatives by treatment of aldehyde and indole using PEG as a recyclable medium without the addition of any additive or organic co-solvent. Mild reaction conditions, inexpensive reaction medium, operational simplicity and high yields are the advantages of the protocol.

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