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$Zn(OAc)_2 \cdot 2H_2O$ -Catalyzed, Simple, and Clean Procedure for the Synthesis of 2-Substituted Benzoxazoles Using a Grindstone Method

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Zn(OAc)₂ · 2H₂O-CATALYZED, SIMPLE, AND CLEAN PROCEDURE FOR THE SYNTHESIS OF 2-SUBSTITUTED BENZOXAZOLES USING A GRINDSTONE METHOD

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GRAPHICAL ABSTRACT



 $R=H, Cl, CH_3, OCH_3, NH_2, OH$

yield 84-95%

Abstract $Zn(OAc)_2 \cdot 2H_2O$ efficiently catalyzes the condensation reaction between 2-aminophenol and various araldehydes to afford the 2-substituted benzoxazoles in good to excellent yields. The remarkable features of this protocol are simple and mild reaction conditions, use of readily available catalyst, and shorter reaction time, and in addition the reaction proceeds just by grinding the substrates and catalyst without any solvent and hence matches the green chemistry protocols.

Keywords 2-Aminophenol; araldehydes; benzoxazoles; grindstone method; solvent-free condition; $Zn(OAc)_2 \cdot 2H_2O$

INTRODUCTION

Synthesis of 2-substituted-benzoxazoles has attracted interest in diverse areas of chemistry.^[1] These heterocycles have shown different pharmacological activities such as antiviral,^[2] antimicrobial,^[3] anti-Parkinson,^[4] anticancer,^[5] and antibiotic^[6] properties. The benzoxazole scaffold is also found in many biologically active compounds such as elastase inhibitors^[7] and H₂ antagonists.^[8]

Synthetic routes to get 2-substituted benzoxazoles typically involve direct coupling of a carboxylic acid or carboxylic acid derivatives with 2-aminophenol in the presence of a strong acid at high temperature. A two-step procedure is also developed in which 2-aminophenol is treated with 1equivalent of an acid chloride, and the resulting mono-*N*-acylated-2-aminophenol is then treated with a variety of reagents including carboxylic acids,^[9] orthoesters,^[10] acid chlorides,^[11] nitriles,^[12]

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Scheme 1. Zinc acetate-catalyzed synthesis of benzoxazoles.

amides,^[13] aldehydes,^[14] or esters.^[15] Beckmann rearrangement of 2-acylphenol oximes^[16] and photocyclization of phenolic Schiff bases^[17] are also used for their synthesis. A few pyrolytic methods for the conversion of diacylated-2-aminophenols into 2-substituted-benzoxazoles also appear in the literature.^[18] Benzoxazoles have normally been synthesized in nonpolar high-boiling solvents such as toluene and xylene^[19] in polar solvents with high boiling points (e.g., sulfolane), and in other solvents such as dichloroethane, dichlorobenzene, and 1,4-dioxane.^[20] It is well known that the solvents used are hazardous, and all these procedures require stoichiometric or excess amounts of reagents to effect the reactions. Many of the procedures produce toxic or environmentally problematic by-products, often involve laborious workup procedures, and/or suffer from poor yields. Therefore, development of more convenient, environmentally friendly, and practical synthetic methods for benzoxazoles still remains an active area of research.

In continuation of our work to explore the utility of simple, one-pot, solvent-free, and solid-phase grinding method (the grinding method has been used by us in the synthesis of biologically important bis(indolyl)methanes^[21] and 4-arylidine-2-phenyl-5(4*H*)-oxazolones^[22]), we have synthesized benzoxazoles by grinding 2-aminophenol with various araldehydes in the presence of $Zn(OAc)_2 \cdot 2H_2O$ as catalyst (Scheme 1).

RESULTS AND DISCUSSION

By grinding thoroughly a mixture of 2-aminophenol with various araldehydes in the presence of $Zn(OAc)_2 \cdot 2H_2O$ using a pestle and mortar at room temperature in an open atmosphere, benzoxazoles were formed in excellent yield within 5 min. To ascertain the optimum conditions, a series of preliminary experiments were carried out using anisaldehyde as model substrate; the reactants were initially ground without any catalyst, but no formation of the product was observed. Then, we decided to use a catalyst, and a number of acidic catalysts were tried for the purpose. When $Zn(OAc)_2 \cdot 2H_2O$ was employed, we got very good results.

Encouraged by these preliminary results, we explored the possibility of generating a small library of benzoxazoles, and the results are presented in Table 1. From Table 1, it is clear that both aldehydes bearing electron-donating groups (entries 2–4 and 8–10) and electron-withdrawing groups (entries 6–8) gave corresponding benzoxazoles in good to excellent yields (84–95%). The structures of all the products were determined from their spectroscopic data, by comparison of the physical

Entry	Aldehyde (2)	Product ^b	Time (min)	Yield (%)
1	C ₆ H ₅ CHO	3a	4	92
2	4-MeO-C ₆ H ₄ CHO	3b	3	95
3	2-MeO-C ₆ H ₄ CHO	3c	4	87
4	4-Me-C ₆ H ₄ CHO	3d	5	85
5	3-Me-C ₆ H ₄ CHO	3e	4	92
6	2-NO ₂ -C ₆ H ₄ CHO	3f	5	90
7	4-Cl-C ₆ H ₄ CHO	3g	5	95
8	2,4-Cl ₂ -C ₆ H ₃ CHO	3h	4	89
9	4-NH ₂ -C ₆ H ₄ CHO	3i	3	89
10	4-HO-C ₆ H ₄ CHO	3j	4	90
11	2-HO-C ₆ H ₄ CHO	3k	4	84
12	Furyl-CHO	31	5	87

 Table 1. Synthesis of 2-substituted-benzoxazoles^a

^{*a*}Reaction condition: Aldehyde (1 mmol), 2-aminophenol (1 mmol), and $Zn(OAc)_2 \cdot 2H_2O$ (0.5 mmol) were ground using a pestle and mortar at rt until the overall mixture turned into a solid.

^bYields refer to pure isolated products.



Scheme 2. Plausible mechanism for the formation of benzoxazoles.

constants, and on thin-layer chromatography with the samples prepared by the reported methods.

The mechanism of the reaction most likely involves the prior formation of an intermediate imine (A), which may undergo cyclization with the *o*-hydroxyl group present in the 2-aminophenol to give 2-substituted-2,3-dihydro-benzoxazole (B), which by aerial oxidation yield benzoxazoles (4) as shown in Scheme 2.

EXPERIMENTAL

All chemicals used were commercial, and all solvents were distilled before use. Melting points were recorded in open capillaries using a paraffin bath, and corrections are applied wherever necessary. The products were characterized by comparison of their physical data or from their infrared (IR), ¹H NMR, and gas chromatography (GC)–mass spectra with those of known samples. The IR and ¹H NMR spectra of the products were recorded on Shimatzu Fourier transform (FT)–IR 8400 s and Bruker AMX (400-MHz) spectrometers respectively. Yields refer to the isolated yields of the products. GC–mass spectra were obtained using a Shimadzu GC-MS QP 5050A.

General Procedure for the Preparation of 2-Substituted Benzoxazoles

A mixture of araldehyde (1 mmol), 2-aminophenol (1 mmol), and $Zn(OAc)_2 \cdot 2H_2O$ (0.5 mmol, 0.104 g) was thoroughly ground with a pestle in a mortar at room temperature in an open atmosphere until the overall mixture turned into a solid. Grinding was continued until the reaction went to completion (progress of the reaction was monitored by TLC). After completion, the solid was washed with water, and the product was crystallized from rectified spirit or purified by column chromatography using a short silica-gel column.

CONCLUSION

In conclusion, we report a high-yielding, one-pot protocol for the synthesis of benzoxazoles from readily available and inexpensive materials. The valuable features of this method include (i) mild reaction conditions, (ii) a wide range of functional groups are tolerated, (iii) solvent-free reaction, thereby making the purification process simple, and (iv) elimination of solvent waste.

As the reactions work by *grinding* the reactants and the catalyst, there is scope for use of ball mills in the future for preparing benzoxazoles on a large scale.

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