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Der Pharma Chemica, 2012, 4 (2):761-766
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Direct and practical synthesis of 2-Arylbenzoxazoles promoted by Silica supported sodium hydrogen sulphate

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ABSTRACT

Benzoxazole derivatives have been prepared through the reaction of 2-Amino phenols and aldehydes in the presence of catalytic amount of Silica supported sodium hydrogen sulphate ($NaHSO_4$-SiO_2) under refluxing in Dioxane solvent to obtained excellent yields.

Key words: Benzoxazole derivatives, 2-Amino phenols, aldehydes, recyclable catalyst.

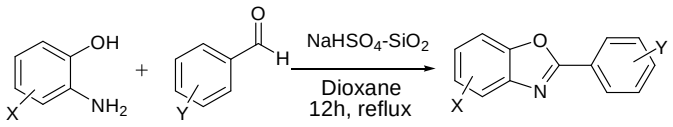
INTRODUCTION

Benzoxazole ring moieties are often found in compounds that exhibit biological activities, including antitumor, antimicrobial, and antiviral properties.[1-4]

There are two general methods for synthesizing 2-substituted benzoxazoles. One is the coupling of 2-amino phenols with carboxylic acid derivatives and acyl chlorides, which is either catalyzed by strong acids[5] (or) requires microwave conditions.[6-7] The other is the oxidative cyclization of phenolic Schiff bases derived from the condensation of 2-amino phenols and aldehydes. In the latter reactions, various oxidants such as DDQ,8 $Mn(OAc)_3$,[9] $PhI(OAc)_2$,[10] $Th^+.ClO_4^-$,[11] $BaMnO_4$,[12] NiO_2,[13] and $Pb(OAc)_4$[14] have been used. However all of these oxidants are required in stoichiometric or excess amounts relative to their respective substrates. Therefore a more effective process is needed.

In recent years, Heterogeneous catalysts have gained imp-ortance in several organic transformations due to their inte-resting reactivity as well as for economic and environment-tal reasons. Recent works[15-19] and their applications with this heterogeneous catalysts we observed that Silica supported sodium hydrogen sulphate is highly efficient catalyst[20-24] for synthesis of substituted benzoxazoles through the reaction of aldehydes and 2-amino phenols under reflux in dioxane solvent. The catalyst $NaHSO_4$-SiO_2 can easily be prepared[25] from the readily available $NaHSO_4$ and silica gel (230-400 mesh) and these are inexpensive and nontoxic as the reaction is heterogeneous in nature the catalyst can easily be removed by simple filtration**.**

Scheme 1



MATERIALS AND METHODS

Experimental procedure

Physical measurements and materials

All ^{1}H NMR spectra were recorded on 400 MHz Varian FT-NMR spectrometers. All chemical shifts are given as δ value with reference to Tetra methyl silane (TMS) as an internal standard. Products were purified by flash chromatography on 100-200 mesh silica gel. The chemicals and solvents were purchased from commercial suppliers either from Aldrich, Spectrochem and they were used without purification prior to use.

General procedure for the synthesis of benzoxazoles

A mixtue of 2-Amino phenol (1 mmol), benzaldehyde (1.2 mmol) and $NaHSO_4$-SiO_2 (25 Wt %) in Dioxane (4 ml) was placed in a 50 ml round bottom flask and stirred at reflux for 12h. The progress of the reaction was monitored by TLC Hexane: EtOAc (4:1) after completion of the reaction, the reaction mixture was cooled and treated by dilution with EtOAc and the catalyst was removed by filtration. Obtained filtrate was washed with diluted solution of 1N NaOH, brine solution and dried over Na_2SO_4 and evaporated under vacuum. Obtained crude residue was purified by column chromatography to give 2- substituted benzoxazoles.

2-Phenylbenzoxazole:[26] This compound was obtained as white solid, m.p. 102-104^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.27-8.24 (m, 2H), 7.79-7.76 (m, 1H), 7.60-7.57 (m, 1H), 7.54-7.51 (m, 3H), 7.38-7.32 (m, 2H); (LC-MS) m/z: 196.20 $[M+H]^+$

2-(2-Methoxyphenyl)benzoxazole:[27] This compound was obtained as white solid, m.p. 54-56^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.13 (d, *J* = 8.8 Hz, 1H), 7.83-7.80 (m, 1H), 7.60-7.57 (m, 1H), 7.51-7.47 (m, 1H), 7.35-7.32 (m, 2H), 7.13-7.07 (m, 2H), 4.02 (s, 3H) ; (LC-MS) m/z: 226.10 $[M+H]^+$

2-(3-Methoxyphenyl)benzoxazole:[28] This compound was obtained as white solid, m.p. 70-73^{o}C; ^{1}H NMR ($CDCl_3$): δ 7.86-7.76 (m, 3H), 7.60-7.57 (m, 1H), 7.43 (t, J = 8 Hz, 1H), 7.36-7.34 (m, 2H), 7.10-7.07 (m, 1H), 3.92 (s, 3H); (LC-MS) m/z: 226.23 $[M+H]^+$

2-(4-Methoxyphenyl)benzoxazole:[26]This compound was obtained as white solid, m.p. 97-99^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.20 (d, J = 9.2 Hz, 2H), 7.74-7.72 (m, 1H), 7.56-7.54 (m, 1H), 7.35-7.31 (m, 2H), 7.03 (d, J = 9.2 Hz, 2H), 3.89 (s, 3H); (LC-MS) m/z: 226.23 $[M+H]^+$

2-(2-Chlorophenyl)benzoxazole:[29] This compound was obtained as white solid, m.p. 70-73^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.15 (dd, *J* = 1.6, 5.6 Hz, 1H), 7.87-7.83 (m, 1H), 7.64-7.61 (m, 1H), 7.59-7.56 (m, 1H), 7.48-7.37 (m, 4H); (LC-MS) m/z: 230.12 $[M+H]^+$

2-(3-Chlorophenyl)benzoxazole:[29] This compound was obtained as white solid, m.p. 131-133^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.26 (s, 1H), 8.16-8.13 (m, 1H), 7.80-7.77 (m, 1H), 7.61-7.58 (m, 1H), 7.52-7.44 (m, 2H), 7.39-7.37 (m, 2H); (LC-MS) m/z: 230.12 $[M+H]^+$

2-(2-Bromophenyl)benzoxazole:[27] This compound was obtained as white solid, m.p. 53-56^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.06 (d, J = 8 Hz, 1H), 7.86-7.83 (m, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.63-7.60 (m, 1H), 7.48-7.32 (m, 4H); (LC-MS) m/z: 273.95, 275.90 $[M+H]^+$

2-(2-Fluorophenyl)benzoxazole:[28] This compound was obtained as white solid, m.p. 92-94^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.24-8.22 (m, 1H), 7.85-7.82 (m, 1H), 7.63-7.61 (m, 1H), 7.54-7.52 (m, 1H), 7.39-7.37 (m, 2H), 7.33-7.26 (m, 2H); (LC-MS) m/z: 214.16 $[M+H]^+$

2-*o*-tolylbenzoxazole: [30] This compound was obtained as off white solid, m.p. 63-66^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.18-8.16 (m, 1H), 7.81-7.79 (m, 1H), 7.60-7.58 (m, 1H), 7.33-7.41 (m, 5H), 2.81 (s, 3H); (LC-MS) m/*z:* 210.14 $[M+H]^+$

2-*p*-tolylbenzoxazole:[26] This compound was obtained as white solid, m.p. 114-116^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.15 (d, *J* = 8 Hz, 2H), 7.77- 7.75 (m, 1H), 7.58-7.56 (m, 1H), 7.35-7.32 (m, 4H), 2.44 (s, 3H); (LC-MS) m/*z:* 210.20 $[M+H]^+$

2-(furan-2-yl)benzoxazole:[26] This compound was obtained as white solid, m.p. 85-87^{o}C; ^{1}H NMR ($CDCl_3$): δ 7.77-7.75 (m, 1H), 7.68-7.67 (m, 1H), 7.58-7.55 (m, 1H), 7.37-7.35 (m, 2H), 7.28 (d, J = 3.6 Hz, 1H), 6.62 (dd, *J* = 3.2, 2 Hz, 1H); (LC-MS) m/*z:* 186.02 $[M+H]^+$

2-(thiophen-2-yl)benzoxazole:[26] This compound was obtained as white solid, m.p. 104-107^{o}C; ^{1}H NMR ($CDCl_3$): δ 7.92-7.91 (m, 1H), 7.75-7.72 (m, 1H), 7.57-7.54 (m, 2H), 7.36-7.33 (m, 2H), 7.21-7.19 (m, 1H); (LC-MS) m/*z:* 202.06 $[M+H]^+$

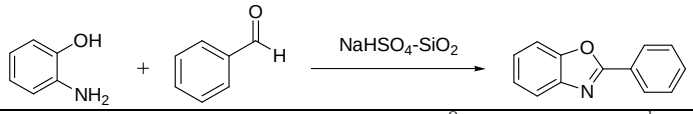
5-methyl-2-phenylbenzoxazole:[29] This compound was obtained as white solid, m.p. 102-104^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.26-8.21 (m, 2H), 7.55 (s, 1H), 7.51-7.46 (m, 3H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.16-7.14 (m, 1H), 2.43 (s, 3H); (LC-MS) m/*z:* 210.20 $[M+H]^+$

5-nitro-2-phenylbenzoxazole;[30] This compound was obtained as white solid, m.p.166-169^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.66 (d, J = 2.4 Hz, 1H), 8.33 (dd, *J* = 6.8, 2 Hz, 1H), 8.28 (d, *J* = 6.4 Hz, 2H), 7.69 (d, J = 9.2 Hz, 1H), 7.62-7.57 (m, 3H); (LC-MS) m/*z:* 241.21 $[M+H]^+$

RESULTS AND DISCUSSION

In our preliminarily investigation on the model reaction of 2- amino phenol and benzaldehyde, it was found that the reaction could be finished under very simple reaction conditions in the presence of catalytic amount of $NaHSO_4$-SiO_2 in reflux of dioxane solvent, which gives the desired benzoxazole product in good yield.

Table 1- optimization of the reaction conditions[a]



Entry	Solvent	Time /Temp(^{O}C)	Yield (%)[b]
1	Dioxane	12 h/reflux	90
2	DMSO	12 h/120	59
3	DMF	12 h/120	28
4	THF	12 h/reflux	81
4	*p*-Xylene	12 h/120	61
5	Toluene	12 h/reflux	58
6	1,2Dichloroethane	12 h/reflux	55
7	Ethanol	12 h/reflux	70
8	Solvent-free	12 h/100	63

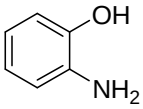
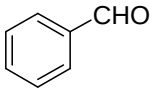
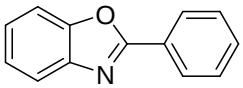
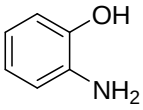
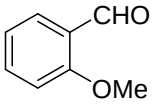
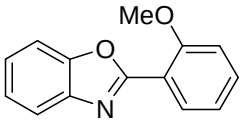
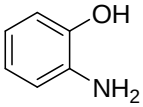
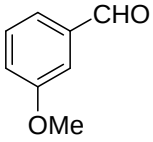
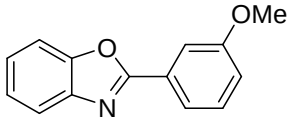
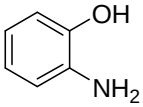
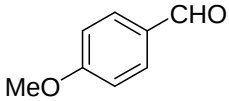
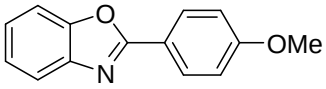
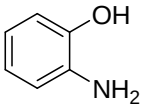
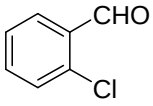
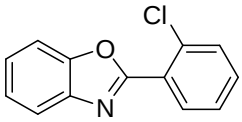
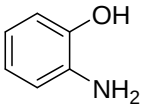
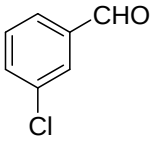
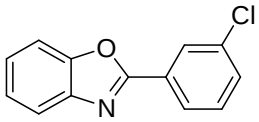
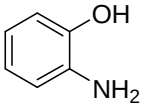
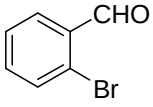
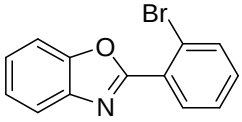
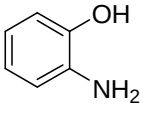
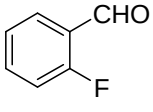
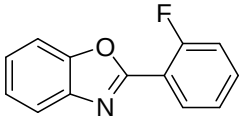
[a]*Reaction conditions: 2-Amino phenol (1 mmol) , Benzaldehyde (1.2mmol) , $NaHSO_4$-SiO_2 (25 Wt%) stirred in solvent (3 ml) at the temperature and time indicated in Table-1.* [b]*Isolated yield.*

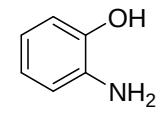
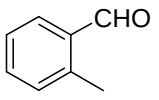
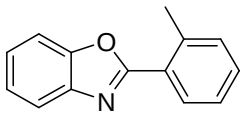
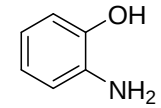
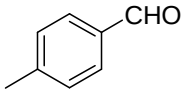
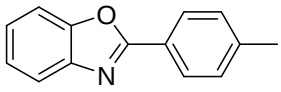
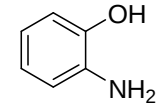
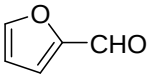
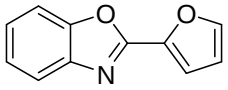
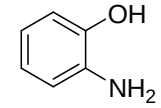
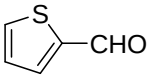
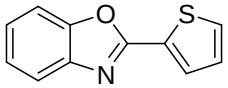
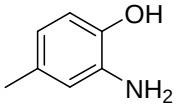
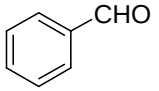
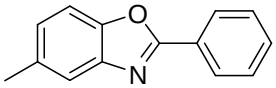
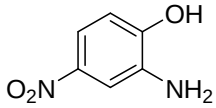
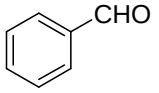
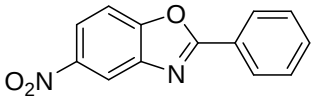
The effect of solvent, catalyst, reaction temperature and time on the reaction was systematically investigated and the results were summarized in Table-1. As can be seen from Table-1, the solvent play an important role in the model reaction, it was found that dioxane is the best one among the solvents tested, and the reaction proceeded smoothly in dioxane and gave the desired product in 90% yield, while DMF afforded the product only in 28%, use of DMSO, THF, *p*- Xylene ,Toluene, 1,2-dichloroethane and ethanol as solvents led to slower reactions and 63% yield of model product was isolated in solvent-free reaction condition. The optimized reaction conditions for the reaction were found to be $NaHSO_4$-SiO_2 under reflux in dioxane solvent for 12h.

Having established the optimized reaction conditions, we turned over attention to explore the scope of this protocol. The results are listed in Table-2. As shown in Table-2, in the most of cases 2-amino phenol reacted with a wide variety of substituted benzaldehydes completely and afforded the corresponding benzoxazoles in good to excellent yields. Substituted benzaldehydes containing electron-donating (or) electron-withdrawing groups on the benzene rings reacted with 2-amino phenol smoothly under optimal reaction conditions to give the desired products. But in case of substituted 2-Amino phenol with a strong electron-with drawing group, such as nitro group on the benzene ring, showed lower reactivity and obtained only 52% yield respectively. (Table-2, entry14).

The reusability of the catalyst is an important factor from economical and environmental point of views and has attracted much attention in recent years. Therefore, the reusability of silica supported sodium hydrogen sulphate was examined in the reaction of simple benzaldehyde with 2-amino phenol under optimized reaction conditions. As $NaHSO_4$-SiO_2 is a heterogeneous catalyst, it was separated by simple filtration after dilution of the reaction mixture with EtOAc. The filtered catalyst was dried at 100^{o}C and reused. (Table-3) The results showed that the catalyst can be used 3 times without loss of its activity.

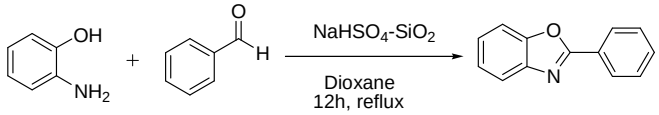
Table 2 – Synthesis of benzoxazoles from 2-Amino phenols and aldehydes[a]

Entry	2-Amino phenol	Aldehyde	product	Yield (%)[b]
1				90
2				79
3				86
4				92
5				76
6				79
7				72
8				74

9				79
10				89
11				92
12				94
13				89
14				52

[a]Reaction conditions: 2-Amino phenol (1 mmol) , aldehyde (1.2 mmol) , $NaHSO_4$-SiO_2 (25 Wt%) was stirred for 12 h under reflux in Dioxane solvent. [b]Isolated yield.

Table 3- Investigation of reusability of $NaHSO_4$-SiO_2 in the synthesis of simple benzoxazole.



Run no	1	2	3
Yield(%)	93	88	79

CONCLUSION

In conclusion we have developed a simple, inexpensive and efficient protocol for the synthesis of benzoxazoles by using various 2-amino phenols and aldehydes as the substrates in the reflux condition of dioxane solvent. The reactions were performed smoothly to generate the corresponding products in high yields under safe experimental conditions and the procedure is simple and convenient. This method offers one of the important motifs for synthesis of benzoxazoles natural products, biologically active compounds and pharmaceutical agents.

Acknowledgments
We sincerely thank the RA chem. Pharma Ltd for financial support and encouragement. Support from the analytical de-partment is also acknowledged.

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