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Antimony chloride immobilized on neutral alumina: an efficient catalyst for the solvent-free selective synthesis of 2-substituted benzoxazoles

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A B S T R A C T

Synthesis of 2-substituted benzoxazoles from 2-amino phenol and aromatic aldehydes in an excellent yield using $SbCl_3$–Al_2O_3 as catalyst with microwave (MW) irradiation under solvent-free conditions. The present methodology shows some advantages such as short reaction times and enhanced selectivity under solvent-free conditions.

Keywords: Benzoxazoles, microwave, Lewis acid, selectivity

A R T I C L E I N F O

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1. Introduction

Benzoxazoles [1] are an important class of heterocyclic compounds in which a benzene fused oxazole ring structure. Benzoxazole finds use in research as a starting material for the synthesis of larger, usually bioactive structures. Its aromaticity makes it relatively stable, although as a heterocyclic, it has reactivesites which allow for functionalization. The benzoxazole and their derivatives exhibit wide range of biological activities such as antifungal [2], antihistaminic [3], cyclooxygenase inhibiting [4], antitumor [5], anticonvulsant [7], hypoglycaemic [8], anti-antiulcer [6], inflammatory [9,10] and cytotoxic activity [11,12], potential activity with lower toxicities in the chemotherapeutic approach in man [13,14]. Oxazole and its derivatives are used as building block for biochemicals and

pharmaceutical as well as in other industrial applications such as pesticides, dyes, fluorescent brightening agents. The synthesis of 1,3-oxazole derivatives are of much interest because of their diverse pharmaceutical applications and interesting chemical properties. 2-substituted benzoxazoles were synthesed mainly in two methods. One is the coupling of o-substituted amino aromatics with carboxylic acid derivatives by using strong acids or microwave conditions. The other is the oxidative cyclization of Phenolic Schiff bases and aldehydes. Different catalysts were also reported for the synthesis of benzoxazole like $Pd(OAc)_2$ [15], $ZrOCl_2.8H_2O$ [16], silica sulfuric acid [17], silicasupported Silicasupported sodium hydrogen sulfate [18], Indion 190 resin [19], ($[Hbim]BF_4$) [20], ethanesulphonic acid [21], $Cu(OTf)_2$ [22], copper(II) oxide nanoparticles [23], PCC-supported silica gel [24], $In(OTf)_3$ [25], $SnCl_2$ [26], DDQ [27], $BF_3.OEt_2$ [28], $Mn(OAc)_3$ [29], $PhI(OAc)_2$ [30], $Th^+.ClO_4^-$ [31], $BaMnO_4$ [32], NiO_2 [33], and $Pb(OAc)_4$ [34]. However there are still some limitations with the existing protocols such as drastic reaction conditions, tedious work-up procedures, poor selectivity, low yields, excess amounts of reagent, use of toxic solvents. Therefore, we wished to explore the usage of $SbCl_3/Al_2O_3$ for the selective synthesis of 2-substitued benzoxazoles by the application of MW technology which shows short reaction times and enhanced selectivity under solvent-free conditions.

2. Materials and Methods

Melting points were measured by using the capillary tube method with an electrothermal method 9200 apparatus. ^{1}H NMR spectra were recorded on BRUKER ADVANCE II 400 NMR Spectrometer using TMS as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$-*d* or DMSO-*d*6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm, DMSO at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm). The mass spectra were obtained on a JEOL 5x102/DA-6000 mass spectrometer. The IR spectra were recorded on Perkin-Elmer spectrum RX IFT-IR System using KBr pellets.

General procedure for the synthesis of benzoxazoles

(3a-h): Freshly distilled aromatic aldehyde (20 mmol), 2-amino phenol (10 mmol) and 3.1 g of catalyst (5 mol% with respect to $SbCl_3$) were mixed thoroughly in a beaker and then irradiated in the MW oven for about 10 min at power level 800 W with 30 sec pause after every one min. Upon completion of the reaction (TLC), the reaction mixture was cooled at rt, ethyl acetate (100 ml) was added, and stirred well followed by filtration through celite under suction. The organic layer was washed with water (2 × 30 ml) and brine (30 ml). After drying over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the residue upon column chromatography affords the pure product.

Spectral data for selected compounds:

2-phenyl benzoxazole (3a): yield 93%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29-8.27 (m, 2H), 7.82-7.78 (m, 1H), 7.62-7.58 (m, 1H), 7.56-7.53 (m, 3H), 7.39-7.35 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 150.7, 142.0, 131.5, 128.9, 127.6, 127.1, 125.1, 124.6, 120.0, 110.6 ppm.

2-(4-fluorophenyl)benzoxazole (3b):

Yielded 90%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30-8.25 (m, 2H), 7.80-7.76 (m, 1H), 7.60-7.57 (m, 1H), 7.39-7.35 (m, 2H), 7.25-7.20 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 163.5, 162.1, 150.7, 142.0, 129.9 (d, *J* = 9.0 Hz), 125.1, 124.7, 123.5 (d, *J* = 3.0 Hz), 120.0, 116.2 (d, *J* = 22.0 Hz), 110.6 ppm.

2-(4-chlorophenyl)benzoxazole (3c):

Yield 91%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.4 Hz, 2H), 7.79-7.76 (m, 1H), 7.60-7.58 (m, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.40-7.36 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 150.8, 142.1, 137.8, 129.3, 128.9, 125.7, 125.4, 124.8, 120.2, 110 ppm.

2-(4-bromophenyl)benzoxazole (3d):

Yield 90%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 7.2 Hz, 2H), 7.80-7.75 (m, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.60-7.56 (m, 1H), 7.39-7.35 (m, 2H). ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 150.7, 142.0, 132.2, 129.0, 128.9, 126.2, 126.1, 125.4, 125.1, 124.7, 120.1, 120.0, 110.6 ppm

2-(3-chlorophenyl)benzoxazole (3e):

Yield 84%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 2.0 Hz, 1H), 8.16-8.13 (m, 1H), 7.81-7.77 (m, 1H), 7.62-7.57 (m, 1H), 7.52-7.50 (d, *J* = 8.4 Hz, 2H), 7.40-7.36 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 150.7, 141.9, 135.0, 131.5, 130.2, 128.8, 127.6, 125.6, 125.5, 124.8, 120.2, 110.7 ppm.

2-(3-methoxyphenyl)benzoxazole (3f):

Yielded 86%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.81-7.79 (m, 2H), 7.62-7.59 (m, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.40-7.35 (m, 2H), 7.12-7.09 (m, 2H), 3.94 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 159.9, 150.7, 142.0, 130.0, 128.3, 125.2, 124.6, 120.1, 120.0, 118.4, 111.8, 110.6, 55.5 ppm.

2-(p-tolyl)benzoxazole (3g):

Yield 92%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.4 Hz, 2H), 7.78-7.76 (m, 1H), 7.59-7.57 (m, 1H), 7.36-7.33 (m, 4H), 2.45 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 150.7, 142.1, 129.6, 127.6, 124.9, 124.5, 124.3, 119.8, 110.5, 21.7 ppm.

2-(4-(trifluoromethyl) phenyl)benzoxazole (3h):

Yield 90%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.0 Hz, 2H), 7.84-7.79 (m, 3H), 7.64-7.60 (m, 1H), 7.44-7.38 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 150.8, 141.9, 133.1, 132.8, 130.4, 127.8, 126.0, 125.9, 125.9, 125.8, 125.1, 124.9, 122.4, 120.4, 110.8 ppm.

2-(4-methoxyphenyl)benzoxazole (3i):

Yield 93%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.8 Hz, 2H), 7.76-7.73 (m, 1H), 7.57-7.55 (m, 1H), 7.36-7.30 (m, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 3.90 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 162.3, 150.6, 142.2, 129.3, 124.6, 124.4, 119.7, 119.6, 114.3, 110.3, 55.4 ppm.

4-(benzoxazol-2-yl)benzonitrile (3j):

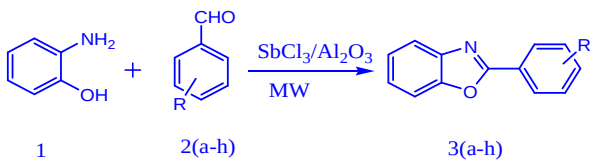
Yield 89%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 8.8 Hz, 2H), 7.85-7.82 (m, 3H), 7.65-7.62 (m,

1H), 7.46-7.40 (m, 2H).ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 150.9, 141.8, 132.7, 131.1, 127.9, 126.2, 125.1, 120.6, 118.2, 114.7, 110.9 ppm.

3. 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 $SbCl_3/Al_2O_3$, which gives the desired benzoxazole product in good yield (Scheme 1). In order to investigate the scope of the reaction, different substituted aldehydes were employed and the results are summarized in Table 1. The optimized reaction conditions for the reaction were found to be $SbCl_3/Al_2O_3$ under room temperature. $SbCl_3/Al_2O_3$ have proved to be an effective catalyst for the synthesis of various 2-substituted-1,3-benzoxazoles and yield is affected by the position of the substituent on aromatic ring of the aldehydes. Meta-substituted aryl aldehyde (3e, 3f), the yield was lower than that when para-substituted aryl aldehydes were used. Also, the results found in Table 1(3d, 3e, 3f) may indicate that the yield is dependent on the electronic nature of the substituent as well.

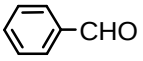
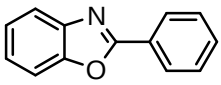
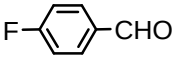
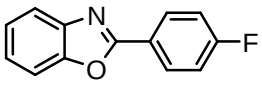
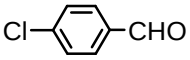
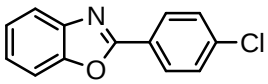
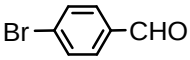
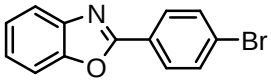
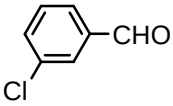
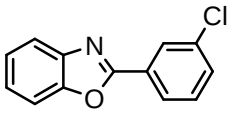
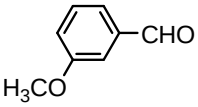
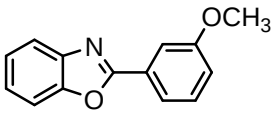
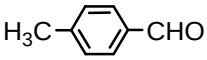
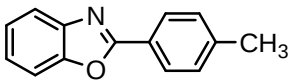
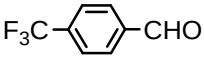
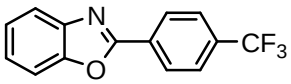
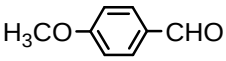
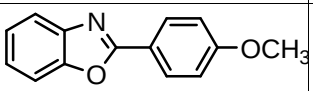
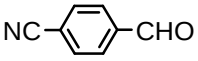
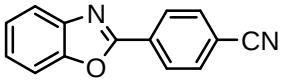
Scheme 1



1 2(a-h) 3(a-h)

Scheme 1: Synthesis of 2-substituted benzoxazoles from 2-aminophenol and aldehydes

Table 1: Synthesis of 2-substituted benzoxazoles from 2-aminophenol and aldehydes

Entry	Aldehydes	Product	Yield (%)
1			93
2			90
3			91
4			90
5			84
6			86
7			92
8			90
9			93
10			89

4. Conclusion

In conclusion, we have demonstrated that 2-substituted benzoxazoles can be synthesized from 2-aminophenols and aldehydes in the presence of $SbCl_3/Al_2O_3$ in good yields. The present protocol is very simple and shows specific advantages, enhanced selectivity under solvent-free conditions and an alternative route to benzoxazole synthesis using 2-aminophenols and aldehydes.

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