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# Strontium Carbonate: As an Efficient, Environmentally free catalyst for the synthesis of 2-Aryl Benzoxazole derivatives

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***Abstract:***
*A Highly Efficient and environmentally benign method has been developed for the synthesis of 2- Aryl benzoxazoles from 2-aminophenol and substituted aldehydes in presence of nanocrystalline strontium carbonate catalyst at room temperature and solvent free conditions.*

***Keywords:*** *2-Aryl Benzoxazole, $SrCO_3$ catalyst, Green chemistry approach*

## I Introduction

The approach to practice medicinal chemistry has developed from an empirical one involving organic synthesis of new compound, based largely on modification of structure of known activity. Numerous heterocyclic compounds, cyclic unhydrates, imides, acetals of dihydroxy acohol, solvents dioxane and THF in all of these the chemistry is essential that of their open chain analog. Heterocyclic intermediates are being used more and more in synthesis as protecting groups, readily generated and readily removed.

2-Aryl benzoxazoles is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and oxazole. Nowadays is a moiety of choice which possesses many pharmacological properties. Benzoxazole derivatives play important role in medical field with so many Pharmacological activities such as antibiotic, antimicrobial, antifungal, antitumor, antiviral, antiulcer, antidiabetic and anticancer activity [1-9]. Benzoxazole also shows some different types of activities such as cathepsin S inhibitors [10,11], selective peroxisome proliferator-activated receptor antagonists [12], HIV reverse transcriptase inhibitors [13,14], estrogen receptor agonists [15] and orexin-1 receptor antagonists [16]. The potency of these clinically useful drugs in treatment of microbial infections and other activities encouraged the development of some more potent and significant compounds., Benzoxazole derivatives have also found application as herbicides and as fluorescent whitening agent dyes [17].

There are numerous methods for synthesizing substituted benzoxazoles, some of the methods for synthesis of benzoxazoles are, coupling of 2-aminophenols with carboxylic acid derivatives, which is either catalyzed by strong acids [18] or requires microwave conditions [19]. The oxidative cyclization of phenolic Schiff bases derived from the condensation of 2-aminophenols and aldehydes. Recently various oxidants such as DDQ [20], pyridinium chlorochromate [21], $Mn(OAc)_3$ [22], $PhI(OAc)_2$ [23], $BaMnO_4$ [24], $NiO_2$ [25], nickel supported silica [26], hydrogen tetrachloroaurate [27], heteropolyacids [28], zinc triflate [29], $PFG_{400}$ [30], SBA-Pr-$SO_3H$ [31], potassium cyanide [32], $ZrOCl_2$ 8H2O [33], ($[Hbim]BF_4$) [34], silica sulfuric acid [35], $Cu(OTf)_2$ [36], $In(OTf)_3$ [37], copper(II) oxide nanoparticles [38], nano $SnO_2$ [39] and $Pb(OAc)_4$ [40] have been used for synthesis of benzoxazoles derrivatives. However, many of these processes suffer from one or more limitations such as drastic reaction conditions, low product yields, tedious work-up procedures, the use of toxic metal salts as catalysts, and relatively expensive reagents. Moreover, these reactions are often carried out in polar solvents such as DMSO leading to tedious work-up procedures. Elimination of organic solvents, high temperature is a frequent goal in green synthesis. Solvent-free organic synthesis decreases both the cost of the synthesis and the amount of waste flow.

In continuation of our studies on developing safe and environmentally benign methodologies for organic synthesis [41-44], herein we report the synthesis of benzoxazole derivatives using $SrCO_3$ nanoparticles as a green catalyst at room temperature and solvent free condition.

## II Experimental

### 2.1. Preparation of Strontium Carbonate

In a typical hydrothermal synthesis, 1 mmol of strontium nitrate, 2 mmol of NaOH and 0.98 mmol of ethylene glycol were dissolved in 100 ml distilled water in a Teflon flask and vigorously stirred for about 15 min for complete mixing. The reaction mixture was then transferred to a Teflon lined stainless steel autoclave (capacity 200 ml). Finally the autoclave was closed and kept inside an electric oven at 100 $^0$C for a definite period of one day. After completion of reaction, white polycrystalline solid product $SrCO_3$ was washed with distilled water and then dried in the oven overnight at 100 $^0$C.

**2.2. General procedure for the synthesis of 2-aryl benzoxazole**

A mixture of 2-aminophenol (1.0 mmol), benzaldehydes (1.0 mmol) and $SrCO_3$ catalyst (0.05 mmol) was grinded by using mortar pestle at room temperature. The progress of the reaction was monitored by thin layer chromatographic technique. After completion of the reaction, the catalyst was filtered off. The pure products were obtained by column chromatography. All products were identified by comparison of their physical and spectroscopic data with those reported for authentic samples. The products were obtained in high yields. Spectral data (FT-IR, $^1$H NMR, $^{13}$C NMR and MS) for all synthesized compounds are reported. The characterization data of some representative synthesized compounds are shown below.

**Selected spectral data**

**2-Phenylbenzoxazole (3a):** FT-IR (KBr): ν = 2972, 1612, 1244, 1037, 805 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$, 400 MHz): δ = 8.21-8.18 (m, 2H, Ar-H), 7.75 (t, J = 7.7 Hz, 1H, Ar-H), 7.55-7.47 (m, 4H, Ar-H), 7.31-7.26 (m, 2H, Ar-H) ppm, $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ = 160.9, 149.7, 140.5, 130.7, 126.9, 125.2, 124.0, 123.5, 123.1, 117.2, 108.6 ppm, MS m/z: calculated 195.21, experimental 196 (M +1).

**2-(4-Nitorophenyl)benzoxazole (3c):** FT-IR (KBr): ν = 1636, 1528, 1340, 1236, 1052 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$, 400 MHz): δ = 8.33 (d, 2H, *J* =8.7Hz), 8.09 (d, 2H, *J* =8.6Hz), 7.37 (d, 1H, *J* =7.8Hz), 7.30 (t, 1H, *J* =7.8Hz), 7.06 (d, 1H, *J* =7.9Hz), 6.92 (t, 1H, *J* =7.7Hz); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) ppm, $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ = 152.9, 151.7, 148.7, 140.1, 133.4, 129.4, 128.5, 123.4, 119.2, 114.4, 113.2 ppm, MS m/z: calculated 240.21, experimental 241 (M +1).

**2-(4-Chlorophenyl)benzoxazole (3f):** FT-IR (KBr): ν = 3304, 29927, 1618, 1572, 1485, 1371, 1232, 1190, 741 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$, 400 MHz): δ = 7.88 (d, 2H, *J* =8.7Hz), 7.49 (d, 2H, *J* =8.6Hz), 7.31 (d, 1H, *J* =7.8Hz), 7.24 (t, 1H, *J* =7.7Hz), 7.04 (d, 1H, *J* =7.9Hz), 6.95 (t, 1H, *J* =7.8Hz) ppm, $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ = 154.2, 151.3, 136.2, 134.2, 133.4, 128.7, 128.0, 127.5, 119.2, 114.7, 113.6 ppm, MS m/z: calculated 229.66, experimental 230 (M +1).

**2-(4-Methylphenyl)benzoxazole (3h):** FT-IR (KBr): ν = 3081, 1633, 1241, 1059 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$, 400 MHz): δ = 8.16 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 4.0 Hz, 1H), 7.58 (d, *J* = 4.5 Hz, 1H), 7.35-7.32 (m, 4H), 2.42 (s, 3H) ppm, $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ = 161.3, 149.7, 140.9, 139.9, 128.6, 125.9, 123.1, 122.8, 121.9, 118.4, 109.7, 20.8 ppm, MS m/z: calculated 209.21, experimental 210 (M +1).

## III Results and Discussion

The crystal phase of synthesized $SrCO_3$ was examined by XRD pattern as shown in Figure 1. The observed intensities of the sharp diffraction peaks indicated that the obtained product has good crystalinity. All of the present peaks in the XRD pattern can be indexed as a pure cubic phase of $SrCO_3$ and it well matches with JCPDS data card number 32-2476. In the XRD pattern no other peaks for impurity were detected. The estimated crystal size from XRD data is found to be 98 nm.

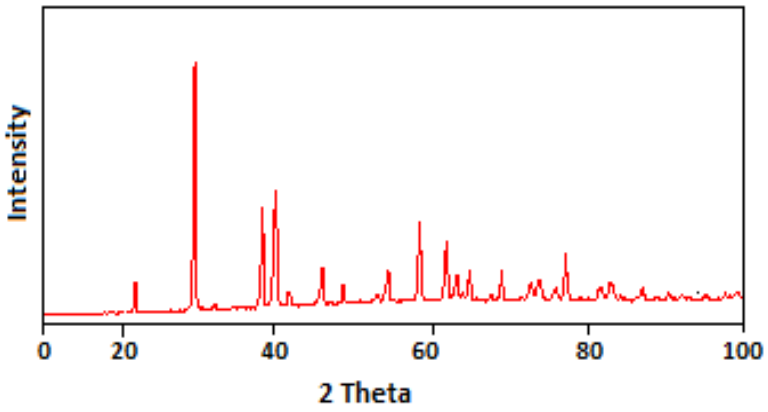



**Fig. 1**: XRD pattern of $SrCO_3$ nanoparticles

Figure 2 gives TEM images shows some of crystals are cubic and rod like. The SAED pattern associated with TEM reveals cubic $SrCO_3$ structure and in total agreement with XRD data. The average particle size of $SrCO_3$ obtained by TEM was found to be 98 nm.

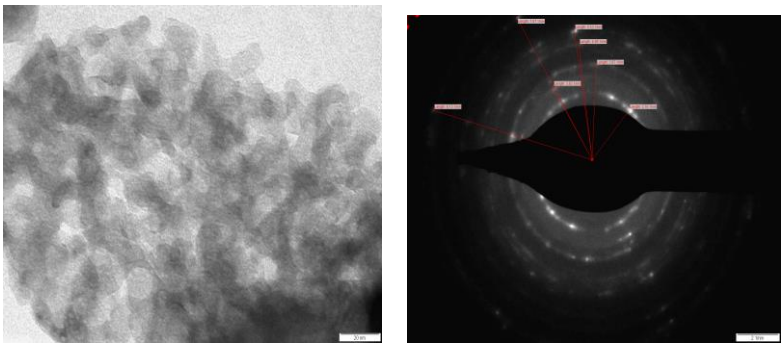


**Fig. 2:** TEM and SAED analysis of $SrCO_3$ nanoparticles.

Figure 3 depicts $N_2$ adsorption –desorption isotherm for synthesized $SrCO_3$. It shows that the synthesized strontium carbonate have typical IV $N_2$ adsorption- desorption isotherm with H1 hysterisis which indicate that sample preserve cylindrical mesopores. The BJH pore size distribution demonstrates that $SrCO_3$ have a narrow pore diameter range. Based on the $N_2$ adsorption-desorption isotherms, surface area ($S_{BET}$) is 178.9 $m^2/g$, the average pore volume (Vp) and pore diameter (dp) were 0.105 cc/g and 54.37 $A^0$ respectively.

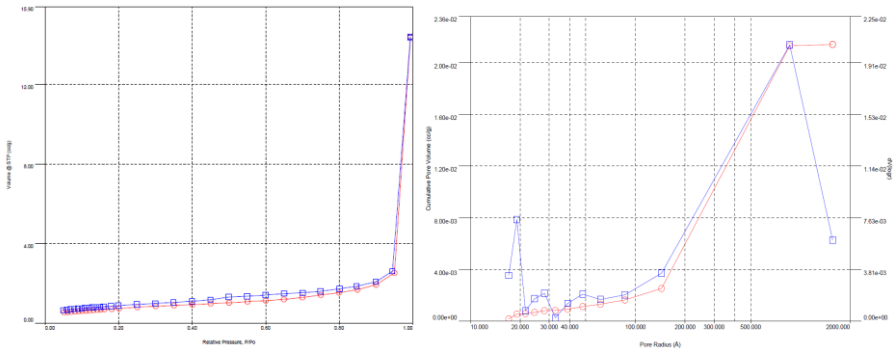


**Fig. 3:** a) BET Surface area and b) Pore volume of $SrCO_3$ nanoparticles

To optimize the amount of catalyst, the yields of reaction using various amounts of catalysts were obtained. The results for synthesis of 2-aryl benzoxazole derivatives from reaction of 2-aminophenol with 4-methoxy

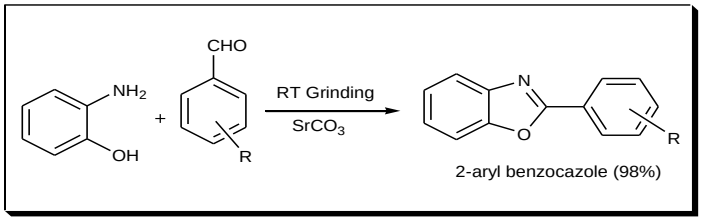
benzaldehyde using different amount of $SrCO_3$ catalyst are shown in Tables 1. It is clear that the yields of reactions in varies with amounts of catalyst, the optimum amount of catalyst was selected as 0.06 mmol for reaction of 2-aminophenol with benzaldehyde. The amount of catalyst greater than 0.06 mmol did not increase the yield of product.

**Table 1:** Effect of amount of catalyst[a]

| Sr. No. | Amount of catalyst (mmol) | Time (min) | Yield (%)[b] |
|---|---|---|---|
| 1 | 0.02 | 45 | 61 |
| 2 | 0.04 | 40 | 76 |
| 3 | 0.06 | 20 | 92 |
| 4 | 0.08 | 20 | 84 |
| 5 | 0.10 | 30 | 90 |

[a]Reaction between benzaldehyde and 2-aminophenol in presense of $SrCO_3$ catalyst.
[b]Isolated yields

In order to study the effect of solvent on the reaction the reaction between 4-methoxy benzaldehyde and 2-aminophenol was carried out with different solvent. In each case the substrates were mixed and grinded with 0.06 mmol of $SrCO_3$ catalyst by mortar and pestle. The solvents like methanol, acetonitrile, dimethylformamide, chloroform, water and solvent free system was used to demonstrate the solvent effect. The formation of product was found to be more facile and proceeded to give the highest yield only under solvent free reaction conditions using grinding (Table 2). The environment of the reaction system in the absence of a solvent is different from that in solution resulting in higher concentration of local reaction sites and an improved global efficiency.




**Scheme:** Synthesis of aryl benzoxazole

To show the general applicability of this method, various aromatic aldehydes were efficiently reacted with one equivalent of 2-aminophenol in the same conditions. These results encouraged us to investigate the scope and the generality of this new protocol for various aromatic aldehydes under optimized conditions. A series of aromatic aldehydes underwent electrophilic substitution reaction with 2-aminophenol to afford a wide range of 2-arylbenzoxazole derivatives in good to excellent yields without any side products. The nature and electronic properties of the substituents on the aromatic ring, affect the conversion rate and aromatic aldehydes having electron-withdrawing groups on the aromatic ring react faster than electron-donating groups. Though meta and para substituted aromatic aldehydes gave good results while ortho-substituted aromatic aldehydes gave lower yields because of the steric effects (Table 3).

**Table 2:** Effect of solvent[a]

| Sr. No. | Solvent | Time (min) | Yield (%)[b] |
|---|---|---|---|
| 1 | MeOH/reflux | 55 | 76 |
| 2 | DMF/reflux | 70 | 82 |

| | | | |
|---|---|---|---|
| 3 | $CHCl_3$/reflux | 65 | 58 |
| 4 | Water/reflux | 85 | 54 |
| 5 | Solvent free/heating | 20 | 89 |
| 5 | Solvent free/grinding | 20 | 92 |

[a]Reaction between benzaldehyde and 2-aminophenol in presense of $SrCO_3$ catalyst.
[b]Isolated yields

**Table 3:** Synthesis of 2-aryl benzoxazole using $SrCO_3$ catalyst

| Entry | Product (R group) | Time (min) | Yield (%)[a] |
|---|---|---|---|
| **3a** | H | 45 | 89 |
| **3b** | 4-$NH_2$ | 35 | 87 |
| **3c** | 4-$N(CH_3)_2$ | 25 | 84 |
| **3f** | 4-OH | 35 | 86 |
| **3g** | 2-OH | 45 | 80 |
| **3h** | 4-$CH_3$ | 30 | 86 |
| **3i** | 4-Cl | 30 | 85 |
| **3j** | 4-F | 25 | 85 |
| **3k** | 4-$OCH_3$ | 20 | 92 |
| **3l** | 2,5-$(OCH_3)_2$ | 30 | 89 |

[a]Isolated yields

Ease of recycling of the catalyst is one of the most advantages of our method. For the reaction of amino phenol with substituted benzaldehyde has no significant loss of the product yield was observed when $SrCO_3$ catalyst was used after four times recycling. The yield of the product in the second, third and fourth was almost the same as that in the first run as shown in Fig 4.

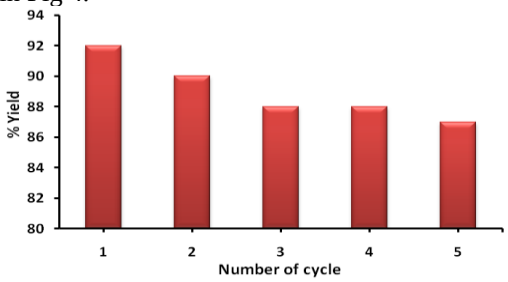



**Fig. 4:** Reusability of catalyst

To show the advantage of the present method a comparison of the efficiency of catalytic activity of the $SrCO_3$ catalyst with several methods is presented in table 4. It is observed that the present method is better to some of the earlier methods reported in terms of catalyst amount, yield and reaction time.

**Table 4.** Screening of catalytic activity of several catalysts[a]

| Entry | Catalyst | Reaction conditions | Time | Yield (%)[b] | Ref. |
|---|---|---|---|---|---|
| 1 | Nickel supported silica | Ethanol/stirring | 1.5 h | 93 | 26 |
| 2 | $PEG_{400}$ | Reflux/80-85°C | 4 h | 90 | 30 |
| 3 | SBA-Pr-$SO_3H$ | Acetic acid/Reflux | 8 h | 91 | 31 |
| 4 | Nano $SnO_2$ | Ethanol/stirring | 21 min | 90 | 39 |
| 5 | $SrCO_3$ catalyst | Grinding/solvent free/r.t | 20 min | 92 | This work |

[a]Reaction between benzaldehyde and 2-aminophenol in presense of $SrCO_3$ nanoparticles

## IV Conclusion

In conclusion, we have successfully synthesized and characterized derivatives of substituted benzoxazole derivatives using a catalytic amount of $SrCO_3$ . This simple procedure is efficient and can be applied to a wide variety of substituted benzaldehydes. Shorter reaction times and excellent product yields make this catalytic system an alternative method for the synthesis of substituted benzoxazole derivatives. The remarkable catalytic activity of $SrCO_3$ catalyst exhibited is convincingly superior to the recently reported other catalytic methods with respect to reaction time, amount of catalyst used. Easy workup and ready availability of the catalyst makes the procedure superior over the existing methods. Environmental acceptability, low cost, high yields and recyclability of the $SrCO_3$ catalyst are the important features of this protocol.

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