Received: 5 October 2016 | Revised: 24 November 2016

DOI: 10.1002/hc.21360

RESEARCH ARTICLE

WILEY Heteroatom Chemistry

One-pot green synthesis of benzoxazole derivatives through molecular sieve-catalyzed oxidative cyclization reaction

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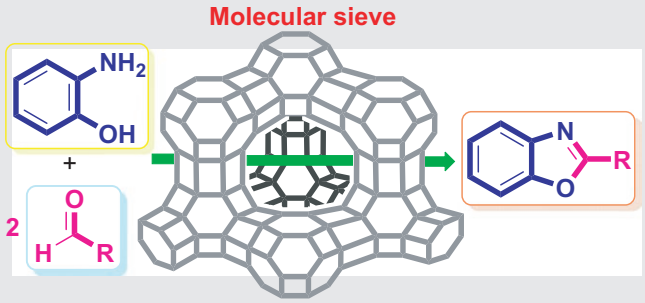
Funding information
Ministry of Science and Technology, Grant/Award Number: MOST 105-2113-M-390-004 and MOST 104-2633-M-390-001; National Science Council, Grant/Award Number: NSC-102-2113-M-390-002

Abstract

An one-pot approach to benzoxazole ring from 2-aminophenol and aldehydes utilizing molecular sieve as the catalyst have been developed. The new oxidative cyclization reaction excluded the usage of hazardous chemical reagents, transition-metal catalysts, chemical oxidants, or strong acids, and, therefore, reduced the production of toxic chemical waste. This offers an environmentally friendly pathway for the synthesis of various benzoxazole derivatives.



1 | INTRODUCTION

The five-member N,O-heteroatom ring of benzoxazole is an important building block in natural products/pharmaceutical targets,[1] polymers,[2] materials,[3] etc. Consequently, developing new methodologies for construction of benzoxazole derivatives have been continuously investigated and reported (Figure 1). In addition to traditional ways using condensation of 2-aminophenol and carboxylic acids/acid halides under strong acids,[4] various organometallic catalyzed reactions were applied in the synthesis of benzoxazole derivatives. For example, oxidative coupling of acetals/imines[5] and cross coupling of amides[6] were reported. Moreover, arylation,[7] one-pot reactions of domino cross coupling,[8] multi-component process,[9] tandem oxidation process,[10] C,C-triple bond cleavage,[11] and dehydrogenative coupling[12] were developed to synthesize benzoxazole derivatives.

However, unlike electrochemical way using anodic coupling reaction of the imine to synthesize benzoxazole ring,[13] those methods usually require to use and/or consume reactive chemical reagents, transition-metal catalysts, chemical oxidants, or strong acids. The resulting toxic chemical wastes cause pollutions to the environment. Organic chemical wastes may be destroyed by burning, and the resulting gas like CO_2 and water will be recycled by plants and other forms of life. However, combustion does not destroy transition metals, and the cost of recycling these transition metals from the chemical wastes is high. Also, when these reactions are applied in the synthesis of pharmaceutical drugs or food additives, accumulation of the remaining hazardous chemical impurities in the bodies may cause unexpected

Contract grant sponsor: Ministry of Science and Technology.

Contract grant number: MOST 105-2113-M-390-004.

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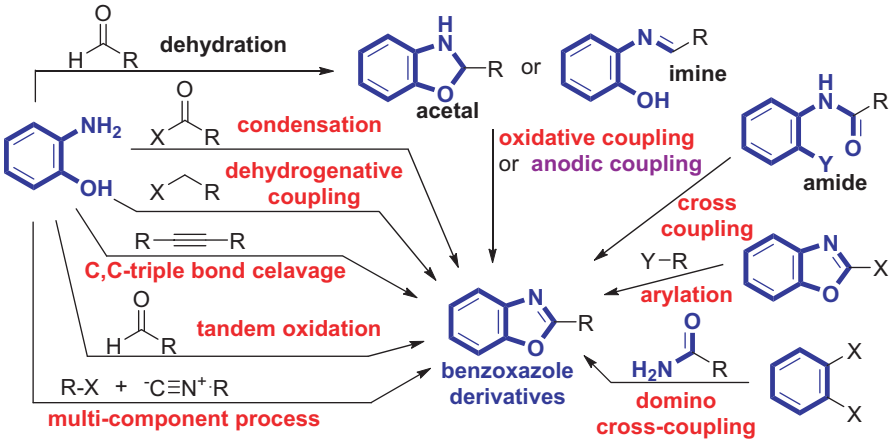


FIGURE 1 Reported methods to synthesize benzoxazole ring

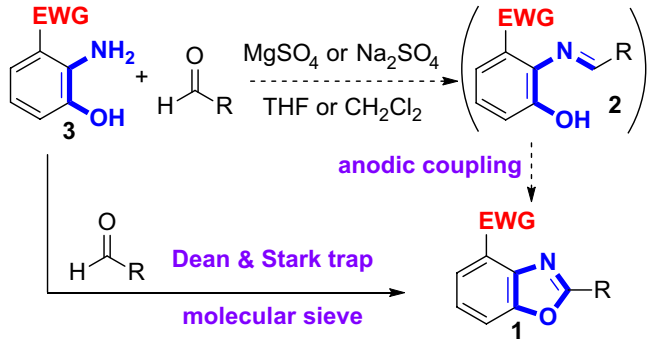


FIGURE 2 Synthesis of imine **2** and benzoxazole **1**

side effects and increase the risk of health problems, especially for the patients taking long-term dosage of medicines.

2 | RESULTS AND DISCUSSIONS

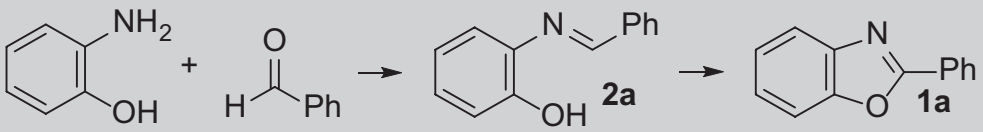
For environmental pollutions and health concerns, developing green pathways of syntheses have attracted more attentions. More efforts in the design of low-pollution pathways have continuously reported. Based on the principle of green chemistry—"design of chemical products and process that reduces or eliminate the use and generation of hazardous substances",[14] we reported a green synthesis of benzoxazole ring **1** through $MgSO_4$ dehydration and an anodic coupling.[13] While this electrochemical pathway was applied in the total synthesis of natural products containing benzoxazole ring, it is hard to obtain imine **2** by $MgSO_4$ dehydration when there is an electron-withdrawing group (EWG) on 2-aminophenol **3** (Figure 2).

Even if using methanol or toluene as the solvent and heating the reaction under refluxing or Dean & Stark trap at 130~150°C, the yield of imine **2** was not high. Surprisingly, when adding molecular sieve to promote the dehydration reaction to form the imine **2**, benzoxazole **1** was obtained directly from 2-aminophenol **3** and aldehydes after heating the reaction to reflux under Dean-Stark trap at 150°C. No additional chemical oxidants were added to oxidize the aldehyde to carboxylic acid, and no other catalysts were used to promote this oxidative cyclization reaction. Comparing to those reported methods in Figure 1 using and/or consuming various reactive chemical reagents and transition-metal catalysts, this synthesis only utilized harmless commercial molecular sieve in the reaction, which offers a simple, low pollution, efficient, low cost, low toxicity pathway to synthesize benzoxazole ring. This matches the goal of *Green Chemistry*. Therefore, we turned to investigate how this one-pot reaction of benzoxazole synthesis proceeded.

In the beginning, toluene was chosen as the solvent and 1.1 equivalent of benzaldehyde were added to react with 2-aminophenol in the reaction. After heating to 150°C and using Dear-Stark trap under argon for 12 hours, only 40% of imine **2a** was obtained (Table 1, entry 1). The yield of imine **2a** was increased to 62% when reaction time was raised to 36 hour (entry 2). Similar yield was obtained while 2.2 equivalent of benzaldehyde was added in the reaction (entry 3). When 3.1 g/mmol of oven-dried 5A molecular sieve was added, 30% of benzoxazole **1a** and 20% imine **2a** were obtained (entry 4). Increasing the amount of molecular sieve to 4.2 or 6.3 g/mmol obtained little progress in yields (entries 5 and 6). Using pure O_2 to facilitate the oxidation of benzaldehyde or imine **2a** observed little more benzoxazole **1a** (entry 7, 38%), but no imine **2a** was obtained. While changing to 3A or 4A molecular sieve (entries 8 and 9), less benzoxazole **1a** was obtained than using 5A molecular sieve. When heating time was raised to 48 hour, similar yield of benzoxazole **1a** was obtained (entry 10).

At this moment, we were not sure whether the low yield of benzoxazole **1a** was caused by evaporation of benzaldehyde with toluene in Dean & Stark trap. The condition was changed to heat the reaction under refluxing at 150°C without Dean & Stark trap, but less amount of benzoxazole **1a** and imine **2a** was obtained (entry 11). While using methanol as the solvent and heating the reaction at 130°C, the yield dramatically dropped and only 5% of imine **2a** was obtained (entry 12). However, when the solvent was changed to xylene

TABLE 1 One-pot synthesis of benzoxazole ring



Entry	Benzaldehyde (eq.)	Molecular sieve (g/mmol)	Solvent and temperature (°C)	Reaction time (h)	Yield
1	1.1	0	Toluene, 150	12	40% (**2a**)
2	1.1	0	Toluene, 150	36	62% (**2a**)
3	2.2	0	Toluene, 150	36	61% (**2a**)
4	1.1	3.1 (5A)	Toluene, 150	36	20% (**2a**) 31% (**1a**)
5	1.1	4.2 (5A)	Toluene, 150	36	21% (**2a**) 31% (**1a**)
6	1.1	6.3 (5A)	Toluene, 150	36	22% (**2a**) 32% (**1a**)
7[a]	1.1	6.3 (5A)	Toluene, 150	36	38% (**1a**)
8	1.1	6.3 (3A)	Toluene, 150	36	33% (**2a**) 14% (**1a**)
9	1.1	6.3 (4A)	Toluene, 150	36	34% (**2a**) 13% (**1a**)
10	1.1	6.3 (5A)	Toluene, 150	48	22% (**2a**) 36% (**1a**)
11[b]	1.1	6.3 (5A)	Toluene, 150	48	18% (**2a**) 29% (**1a**)
12[b]	1.1	6.3 (5A)	Methanol, 130	48	5% (**2a**)
13[b]	1.1	6.3 (5A)	Xylene, 180~190	48	41% (**1a**)
14	1.1	6.3 (5A)	Xylene, 180~190	48	45% (**1a**)
15	**2.2**	**6.3 (5A)**	**Xylene, 180~190**	**48**	**86% (1a)**
16	2.2	5.3 (5A)	Xylene, 180~190	48	80% (**1a**)
17	2.2	4.2 (5A)	Xylene, 180~190	48	74% (**1a**)
18	2.2	3.1 (5A)	Xylene, 180~190	48	70% (**1a**)

[a]Reaction was under O_2.
[b]Only refluxing, 150°C.

and the reaction was heating to reflux at 180-190°C, the yield of benzoxazole **1a** increased to 41% (entry 13). When using Dean-Stark trap of refluxing at 180-190°C, 45% of benzoxazole **1a** was obtained (entry 14).

The content of commercial 5A molecular sieve is [0.7 CaO:0.3 Na_2O:1.0 Al_2O_3:2.0 SiO_2:x H_2O].[15] It is stable and normally does not serve as oxidant or reductant. Comparing the oxidation states of reagents and products, it is an oxidation reaction when the carbonyl carbon of aldehyde becomes the carbon of benzoxazole. If the aldehyde serves as a reactant and an oxidant, it is reasonable to obtain 45% of benzoxazole product (entry 14) when 1.1 equivalent of benzaldehyde was used and no additional oxidation reagent was used. To prove this speculation, 2.2 equivalent of benzaldehyde was added and, inspiringly, 86% of benzoxazole **1a** was obtained directly in one step (entry 15). To search for suitable amount of molecular sieve, 5.3, 4.2 and 3.1 g/mmol of molecular sieve were tested (entries 16, 17 and 18) and 6.3 g/mmol is the best ratio (entry 15).

To further probe whether aldehyde does play dual roles as a reactant/oxidant and molecular sieve serves as a catalyst, we performed the benzoxazole synthesis from the imine **2a** (Table 2). When imine **2a** with 5A molecular sieve in xylene was heated to reflux at 180-190°C and no additional aldehyde was added, only 41% of benzoxazole **1a** was obtained (entry 1). With additional 1.1 equivalent of aldehyde, the yield of benzoxazole **1a** dramatically doubled to 87% (entry 2). These two conditions prove that molecular sieve is not the oxidant to oxidize the imine **2a** to form benzoxazole **1a**. Instead, the results indicate that it may be the additional equivalent of aldehyde to serve as

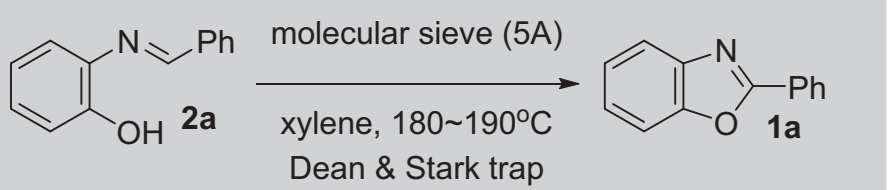


TABLE 2 Synthesis of benzoxazole **1a** from imine **2a**

Entry	Benzaldehyde (eq.)	Molecular sieve (g/mmol)	Reaction time (h)	Yield
1	0	6.3	48	41% (**1a**)
2	**1.1**	**6.3**	**48**	**87% (1a)**
3	1.1	0	48	99% (**2a**)
4	0.55	0	48	99% (**2a**)
5	0.55	6.3	48	66% (**1a**)
6	1.1	6.3	24	72% (**1a**)
7	1.1	6.3	12	60% (**1a**)
8[a]	1.1	0	48	N/A

[a]1.0 equivalent of $LiOCH_3$ was added.

the oxidant. When no molecular sieve was added, 99% of imine **2a** was recovered, even if benzaldehydes were added (entries 3 and 4). This further implies that molecular sieve plays an important role of the catalyst for oxidative cyclization reaction to form benzoxazole **1a** from imine **2a** and a benzaldehyde. Adding molecular sieve but reducing the amount of aldehyde to 0.55 equivalent (entry 5) or reaction time (entries 6 and 7) lowered the yields of benzoxazole **1a**. When 1.0 equivalent of LiOMe was added, only the spot of imine **2a** and a spot with a very low R_f value were shown on TLC plate, the latter of which suggests the formation of N,O-acetal in the reaction, and no benzoxazole **1a** was obtained (entry 8). This proves that it did not go through the pathway of Cannizzaro reaction or Tischchenko reaction, in which the resulting carboxylic acid derivatives from the aldehyde condensed with 2-aminophenol to form benzoxazole **1a**.

From these results, it can almost confirm that the first equivalent of aldehyde is the reactant to form imine **2a**. The molecular sieve works as the catalyst and utilizes the second equivalent of aldehyde as the oxidant to proceed oxidative cyclization of imine **2a** to form benzoxazole **1a**.

To verify whether the second equivalent of benzaldehyde serves as the oxidant, benzyl alcohol product is the evident. Therefore, after refluxing by Dean-Stark trap, the reaction mixture was filtered and washed by xylene. The crude solution and pure benzyl alcohol were tested, respectively, by ESI and CI mass spectrometer. However, no signal of m/z=108 was obtained, even for the pure benzyl alcohol. This might be because low boiling point and tendency to dehydration of benzyl alcohol make it difficult to obtain the molecular ion peak of benzyl alcohol in ESI and CI mass spectrum.

Although benzyl alcohol signal is hard to be detected by mass spectrometer, its existence could not be excluded. Based on previous results, reaction mechanism of molecular sieve-catalyzed oxidative cyclization was proposed (Figure 3). In the beginning, the first equivalent of benzaldehyde condenses with amino group of 2-aminophenol to form the imine **2** during refluxing. Then the weak base of 5A molecular sieve deprotonates the phenol group to form phenolate **4-1**, which favors to form 5-membered ring of N,O-acetal anion **4-2**.[13] Comparing to Na^+ or Ca^{2+} ions, it is more possible that Al^{3+} in molecular sieve plays the role of Lewis acid, which facilitates the reduction of the second equivalent benzaldehyde to benzyl alcohol and the oxidation of N,O-acetal anion to obtain the benzoxazole product under Dean & Stark trap condition.[16]

With the success of benzoxazole synthesis using benzaldehyde, experiments were extended to other aldehydes to synthesize various benzoxazole derivatives (Table 3). Methyl-, methoxy-, and chloro-substituents achieved 66%-85% yield (entries 1-9). The yields for acidic aldehydes of hydroxyl-substituents were 41%-61% (entry 10-11) and benzyloxy-substituent was 66% (entry 12). For the basic aldehydes, the yields were 34%-42% (entry 13-14). As to the alkyl-substituent like cyclohexane, 67% of product **1p** was obtained (entry 15). Heteroatom aldehydes got 22%-89% of benzoxazole **1q-t** (entry 16-19). The low yield for the furan-2-carbaldehyde **1q** might be because the low boiling point (160°C). For aldehydes with nitrogen atom on the ring (**1n**, **1o**, and **1t**), the nitrogen is a better Lewis base to chelate with molecular sieve than the oxygen of carbonyl group of the aldehyde, which may interfere the process of reduction reaction.

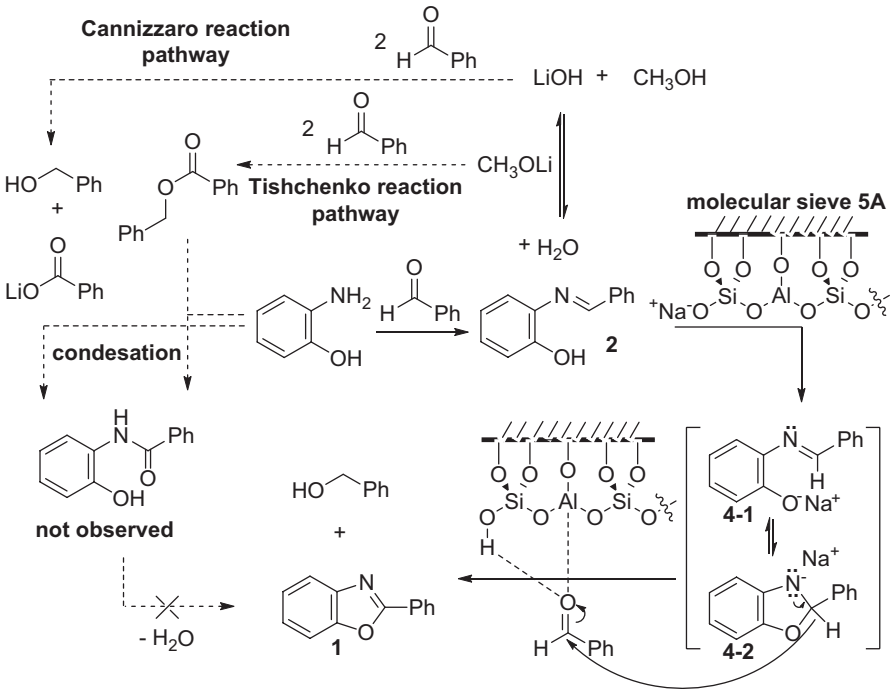


FIGURE 3 Propose reaction mechanism

To date, our newly developed pathway is the first method which do not using and consuming additional chemical reagents in the synthesis of benzoxazole derivatives. Only 2-aminophenol, two equivalents of aldehyde reactant, and non-toxic commercial 5A molecular sieve were added in the reaction. Since hazardous chemical reagents and transition-metal catalysts are not required, their corresponding harmful chemical wastes are excluded then. Also, it simplifies the reaction conditions in the synthesis of benzoxazole derivatives and is no need to use complicated chemical reagents, comparing to other reported methods (Figure 1). This matches the goal of *Green Chemistry*. Moreover, it reduces the risks of remaining transition-metals or other toxic chemicals in the products. This prevents the accumulation of toxic contents for people who take daily food additives or long-term dosage of drugs from artificial synthesis.

In summary, we have developed a clean and one-pot reaction to synthesize benzoxazole derivatives through molecular sieve-catalyzed oxidative cyclization reaction. The new pathway offers an environmentally friendly reaction conditions and excludes the usage of toxic chemical reagents and catalysts. This not only reduces the pollutions of various chemicals in the environment, but also keeps away the toxic chemical contents, like transition metals, in the artificially synthesized products from our diet. Also, the simplified reaction pathway is suitable for industrial large-scale synthesis because the cost of purchasing chemical reagents is saved and the expenses to deal with the resulting chemical wastes are reduced. Further reactions applied in the green synthesis of pharmaceutical drugs are in progress.[17]

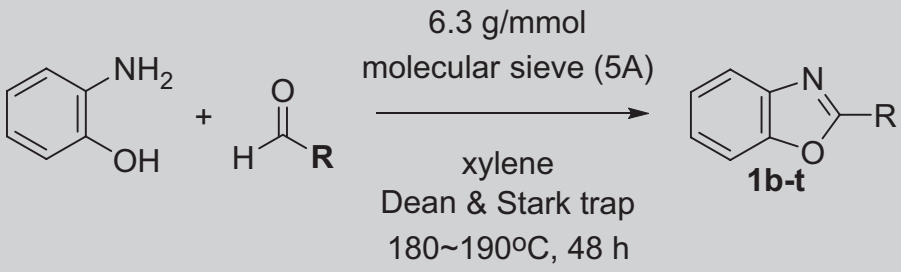
3 | EXPERIMENTAL SECTION

All the chemical reagents were purchased from commercial suppliers (Sigma-Aldrich, Acros, Alfa Aesar, etc.) and used as received, unless otherwise indicated. The molecular sieves (3A, 4A, and 5A) were made by J. T. Baker, and used in the reaction after 96°C oven-dried. Column chromatography separations were performed using silica gel (70-230 mesh). Thin-layer chromatography was carried out on glass plates (pre-coated TLC plates DURASIL-25 UV_{254}). ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded with 300 MHz spectrometers (VARIAN Mercury 300 Plus) in chloroform-*d* or DMSO-d_6. Chemical shifts (δ) are given in parts per million and coupling constants are given as absolute values expressed in Hertz. LRMS and HRMS analyses were performed on Fourier-transfer mass spectrometry (Bruker APEX II) at High Valued Instrument Center of Ministry of Science and Technology in Taiwan.

3.1 | General experiment procedure

Under argon, oven-dried molecular sieve (3A, 4A or 5A) and a stir bar were added to a 100-mL round bottle. After cooled to room temperature, 45 mL anhydrous CH_3OH or distilled solvent (toluene or xylene) was added to dissolve 2-amino-phenol (0.2076 g, 1.8833 mmol) and aldehyde (1.1 or 2.2 equivalent) in the bottle. Then, a 10-mL Dean-Stark receiver, containing oven-dried 5A molecular sieve with a Graham condenser was inserted to the bottle. The resulting

TABLE 3 Synthesis of benzoxazole derivatives



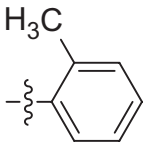
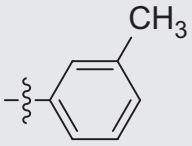
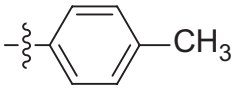
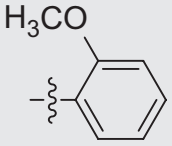
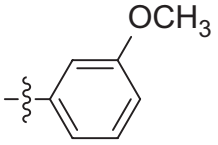
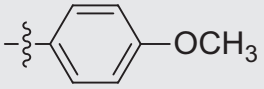
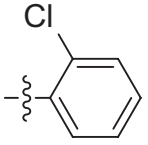
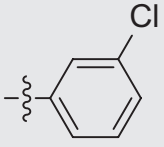
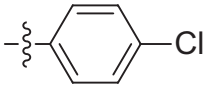
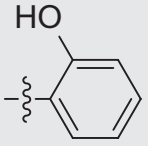
Enrty	Aldehyde, R	Yield
1		74% (**1b**)
2		75% (**1c**)
3		85% (**1d**)
4		78% (**1e**)
5		77% (**1f**)
6		76% (**1g**)
7		72% (**1h**)
8		66% (**1i**)
9		85% (**1j**)
10		41% (**1k**)

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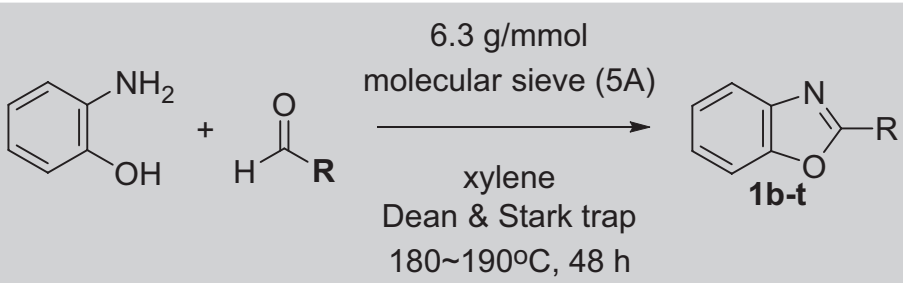
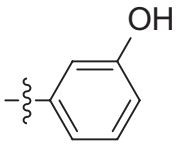
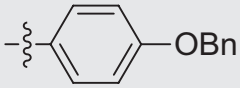
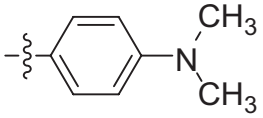
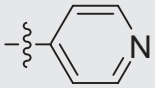
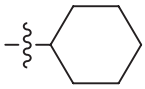
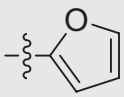
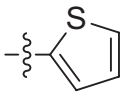
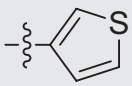
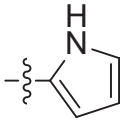
TABLE 3 (Continued)



Enrty	Aldehyde, R	Yield
11		61% (**1l**)
12		66% (**1m**)
13		34% (**1n**)
14		42% (**1o**)
15		67% (**1p**)
16		22% (**1q**)
17		58% (**1r**)
18		89% (**1s**)
19		31% (**1t**)

mixture was stirred very slowly in order not to grind the molecular sieve into powder by stir bar. After heating to refluxing with or without Dean-Stark trap for 12~48 hours [130°C for methanol; 150°C for toluene; 180~190°C for xylene], the solution was filtered and the molecular sieve was thoroughly washed by EtOAc. The filtrate was concentrated and the residue was purified via column chromatography (SiO_2). The elute solutions for column packing was 100% hexane with 10% NEt_3 (no NEt_3 for **1k** and **1l**), and for purification of benzoxazole derivatives (**1a-t**) was mixture of hexane and EtOAc with 5% NEt_3 (no NEt_3 for **1k** and **1l**).

3.2 | 2-phenyl-benzoxazole (1a)[5a]

Elute solution (hexane:EtOAc=10:1 with 5% NEt_3); yield 86%; white solid; mp=95~97°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=8.29-8.23 (m, 2H), 7.82-7.76 (m, 1H), 7.58-7.53 (m, 1H), 7.53-7.47 (m, 3H), 7.36-7.31 (m,

2H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=163.1, 150.8, 142.2, 131.5, 128.9, 127.7, 127.2, 125.1, 124.6, 120.1, 110.6 ppm. IR (KBr): 3059, 1617, 1552, 1471, 1454, 1446, 1343, 1290, 1242, 1052, 923, 744, 702, 688 cm^{-1}. LRMS (ESI): $C_{13}H_9NO$, *m/z*=196 for $[M+H]^+$; HRMS (ESI): $C_{13}H_9NO$, *m/z* calcd. for $[M+H]^+$: 196.0757; found: 196.0758.

3.3 | 2-(2-methyl-phenyl)-benzoxazole (1b)[5a]

Elute solution (hexane:EtOAc=20:1 with 5% NEt_3); yield 74%; yellow solid; mp=58~60°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=8.19 (d, *J*=8.4 Hz, 1H), 7.86-7.78 (m, 1H), 7.65-7.56 (m, 1H), 7.47-7.42 (m, 1H), 7.41-7.35 (m, 4H), 2.83 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=163.6, 150.5, 142.3, 139.0, 132.0, 131.1, 130.1, 126.4, 126.2, 125.2, 124.5, 120.3, 110.6, 22.4. IR (KBr): 3059, 2958, 2924, 2846, 1613, 1550, 1485, 1452, 1239, 1029, 741, 724 cm^{-1}. LRMS (ESI): $C_{14}H_{11}NO$, *m/z*=210 for $[M+H]^+$; HRMS (ESI): $C_{14}H_{11}NO$, *m/z* calcd for $[M+H]^+$: 210.0913; found: 210.0915.

3.4 | 2-(3-methyl-phenyl)-benzoxazole (1c)[5a]

Elute solution (hexane:EtOAc=20:1 with 5% NEt_3); yield 75%; yellow solid; mp=73~76°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=8.10 (s, 1H), 8.06 (d, *J*=7.5 Hz, 1H), 7.83-7.76 (m, 1H), 7.60-7.54 (m, 1H), 7.45-7.37 (t, *J*=7.5 Hz, 2H), 7.37-7.32 (m, 2H), 2.45 (s, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=163.4, 150.8, 142.2, 138.8, 132.5, 128.9, 128.3, 127.1, 125.2, 124.9, 124.7, 120.1, 110.7, 21.5 ppm. IR (KBr): 3048, 2913, 2952, 2852, 1611, 1550, 1474, 1452, 1242, 1175, 1055, 862, 744, 716, 685, 439 cm^{-1}. LRMS (ESI): $C_{14}H_{11}NO$, *m/z*=210 for $[M+H]^+$. HRMS (ESI): $C_{14}H_{11}NO$, *m/z* calcd. for $[M+H]^+$: 210.0913; found: 210.0915.

3.5 | 2-(4-methyl-phenyl)-benzoxazole (1d)[5a]

Elute solution (hexane:EtOAc=20:1 with 5% NEt_3); yield 85%; yellow solid; mp=112~113°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=8.16 (d, *J*=8.1 Hz, 2H), 7.81-7.74 (m, 1H), 7.61-7.55 (m, 1H), 7.38-7.31 (m, 4H), 2.45 (s, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=163.5, 150.9, 142.4, 142.3, 129.9, 127.8, 125.1, 124.7, 124.6, 120.1, 110.7, 21.9 ppm. IR (KBr): 3053, 2958, 2913, 2852, 1620, 1552, 1499, 1449, 1242, 1178, 1055, 820, 744, 736, 724, 498 cm^{-1}. LRMS (ESI): $C_{14}H_{11}NO$, *m/z*=210 for $[M+H]^+$. HRMS (ESI): $C_{14}H_{11}NO$, *m/z* calcd for $[M+H]^+$: 210.0913; found: 210.0915.

3.6 | 2-(2-methoxy-phenyl)-benzoxazole (1e)[5a]

Elute solution (hexane:EtOAc=5:1 with 5% NEt_3); yield 78%; yellow solid; mp=55~57°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=8.10 (dd, *J*=7.8, 1.5 Hz, 1H), 7.84-7.77 (m, 1H), 7.57-7.50 (m, 1H), 7.45-7.37 (td, *J*=7.8, 1.5 Hz, 1H), 7.32-7.25 (m, 2H), 7.06-6.97 (m, 2H), 3.93 (s, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=161.5, 158.4, 150.2, 142.1, 132.7, 131.2, 124.9, 124.2, 120.6, 120.1, 116.0, 112.0, 110.4, 56.1 ppm. IR (KBr): 3048, 2958, 2924, 2835, 1614, 1597, 1583, 1550, 1536, 1494, 1483, 1452, 1432, 1309, 1264, 1245, 1122, 1035, 1021, 783, 750, 702 cm^{-1}. LRMS (ESI): $C_{14}H_{11}NO_2$, *m/z*=226 for $[M+H]^+$. HRMS (ESI): $C_{14}H_{11}NO_2$, *m/z* calcd. for $[M+H]^+$: 226.0863; found: 226.0861.

3.7 | 2-(3-methoxy-phenyl)-benzoxazole (1f)[5a]

Elute solution (hexane:EtOAc=5:1 with 5% NEt_3); yield 77%; yellow solid; mp=63~66°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=7.85 (dt, *J*=7.5, 1.3 Hz, 1H), 7.81-7.76 (m, 2H), 7.60-7.55 (m, 1H), 7.45-7.38 (t, *J*=8.0 Hz, 1H), 7.38-7.32 (m, 2H), 7.08 (ddd, *J*=9, 2.3, 1.0 Hz, 1H), 3.89 (s, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=163.1, 160.0, 150.9, 142.2, 130.1, 128.4, 125.3, 124.7, 120.2, 120.1, 118.4, 112.0, 110.7, 55.6 ppm. IR (KBr): 3059, 2997, 2952, 2936, 2829, 1603, 1583, 1552, 1491, 1479, 1452, 1297, 1242, 1041, 867, 761, 744, 683 cm^{-1}. LRMS (ESI): $C_{14}H_{11}NO_2$, *m/z*=226 for $[M+H]^+$. HRMS (ESI): $C_{14}H_{11}NO_2$, *m/z* calcd. for $[M+H]^+$: 226.0863; found: 226.0862.

3.8 | 2-(4-methoxy-phenyl)-benzoxazole (1g)[5a]

Elute solution (hexane:EtOAc=5:1 with 5% NEt_3); yield 76%; white solid; mp=97~98°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=8.19 (d, *J*=9 Hz, 2H), 7.77-7.71 (m, 1H), 7.57-7.51 (m, 1H), 7.35-7.28 (m, 2H), 7.01 (d, *J*=8.7 Hz, 2H), 3.85 (s, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=163.3, 162.4, 150.8, 142.4, 129.5, 124.7, 124.5, 119.8, 119.7, 114.5, 110.5, 55.5 ppm. IR (KBr): 3048, 2975, 2952, 2919, 2840, 1620, 1614, 1606, 1580, 1502, 1455, 1421, 1253, 1242, 1169, 1018, 831, 758, 741, 727, 632, 517 cm^{-1}. LRMS (ESI): $C_{14}H_{11}NO_2$, *m/z*=226 for $[M+H]^+$. HRMS (ESI): $C_{14}H_{11}NO_2$, *m/z* calcd. for $[M+H]^+$: 226.0863; found: 226.0861.

3.9 | 2-(2-chloro-phenyl)-benzoxazole (1h)[5a]

Elute solution (hexane:EtOAc=20:1 with 5% NEt_3); yield 72%; yellow solid; mp=64~66°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=8.11-8.06 (m, 1H), 7.85-7.79 (m, 1H), 7.56-7.52 (m, 1H), 7.50-7.45 (m, 1H), 7.34-7.29 (m, 4H) ppm.

^{13}C-NMR ($CDCl_3$, 75 MHz): δ=160.8, 150.4, 141.6, 133.3, 131.8, 131.7, 131.3, 126.8, 126.1, 125.5, 124.6, 120.4, 110.7 ppm. IR (KBr): 3064, 1611, 1592, 1569, 1552, 1536, 1471, 1452, 1432, 1239, 1083, 1027, 811, 758, 741, 727, 652, 459 cm^{-1}. LRMS (ESI): $C_{13}H_8ClNO$, *m/z*=230 for $[M+H]^+$. HRMS (ESI): $C_{13}H_8ClNO$, *m/z* calcd. for $[M+H]^+$: 230.0367; found: 230.0366.

3.10 | 2-(3-chloro-phenyl)-benzoxazole (1i)[5a]

Elute solution (hexane:EtOAc=5:1 with 5% NEt_3); yield 66%; yellow solid; mp=131~132°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=8.18 (s, 1H), 8.06 (d, *J*=7.5 Hz, 1H), 7.78-7.71 (m, 1H), 7.55-7.49 (m, 1H), 7.46-7.29 (m, 4H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=161.6, 150.8, 141.9, 135.1, 131.5, 130.2, 128.8, 127.6, 125.6, 125.6, 124.8, 120.3, 110.7 ppm. IR (KBr): 3053, 1614, 1572, 1547, 1469, 1452, 1432, 1340, 1295, 1281, 1239, 1192, 1049, 929, 822, 758, 738, 713, 671, 436 cm^{-1}. LRMS (ESI): $C_{13}H_8ClNO$, *m/z*=230 for $[M+H]^+$. HRMS (ESI): $C_{13}H_8ClNO$, *m/z* calcd. for $[M+H]^+$: 230.0367; found: 230.0366.

3.11 | 2-(4-chloro-phenyl)-benzoxazole (1j)[5a]

Elute solution (hexane:EtOAc=10:1 with 5% NEt_3); yield 85%; white solid; mp=147~148°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=8.18 (d, *J*=8.4 Hz, 2H), 7.80-7.74 (m, 1H), 7.60-7.54 (m, 1H), 7.53-7.46 (d, *J*=8.7 Hz, 2H), 7.40-7.33 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=162.2, 150.9, 142.2, 137.9, 129.4, 129.0, 125.8, 125.5, 124.9, 120.3, 110.8 ppm. IR (KBr): 3059, 1614, 1555, 1536, 1483, 1452, 1404, 1343, 1273, 1245, 1091, 1055, 1010, 923, 890, 831, 758, 738, 495 cm^{-1}. LRMS (ESI): $C_{13}H_8ClNO$, *m/z*=230 for $[M+H]^+$. HRMS (ESI): $C_{13}H_8ClNO$, *m/z* calcd. for $[M+H]^+$: 230.0367; found: 230.0367.

3.12 | 2-(benzoxazol-2-yl)phenol (1k)[5d]

Elute solution (hexane:EtOAc=5:1); yield 41%; yellow solid; mp=121~122°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=11.48 (bs, 1H), 8.03 (dd, *J*=8.0, 1.8 Hz, 1H), 7.76-7.71 (m, 1H), 7.64-7.59 (m, 1H), 7.44 (td, *J*=7.8, 1.8 Hz, 1H), 7.41-7.36 (m, 2H), 7.13 (dd, *J*=8.4, 1.1 Hz, 1H), 7.01 (td, *J*=7.2, 1.1 Hz, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=163.1, 158.9, 149.3, 140.2, 133.8, 127.3, 125.6, 125.2, 119.8, 119.5, 117.6, 110.9, 110.8 ppm. IR (KBr): 3059, 1631, 1586, 1544, 1485, 1451, 1259, 1248, 1236, 1049, 738, 704, 683, 669, 464 cm^{-1}. LRMS (ESI): $C_{13}H_9NO_2$, *m/z*=212 for $[M+H]^+$. HRMS (ESI): $C_{13}H_9NO_2$, *m/z* calcd. for $[M+H]^+$: 212.0706; found: 212.0708.

3.13 | 3-(benzoxazol-2-yl)phenol (1l)[12a]

Elute solution (hexane:EtOAc=2:1); yield 61%; white solid; mp=218~222°C.^{1}H-NMR (DMSO-d_6, 300 MHz): δ=9.97 (s, 1H), 7.83-7.74 (m, 2H), 7.67-7.57 (m, 2H), 7.46-7.35 (m, 3H), 7.02 (d, *J*=8.1 Hz, 1H) ppm. ^{13}C-NMR (DMSO-d_6, 75 MHz): δ=162.3, 157.9, 150.2, 141.5, 130.5, 127.5, 125.5, 124.8, 119.8, 119.1, 118.0, 113.6, 110.9 ppm. IR (KBr): 3412, 1650, 1631, 1614, 1597, 1547, 1449, 1298, 1236, 758, 747, 666 cm^{-1}. LRMS (ESI): $C_{13}H_9NO_2$, *m/z*=212 for $[M+H]^+$. HRMS (ESI): $C_{13}H_9NO_2$, *m/z* calcd. for $[M+H]^+$: 212.0706; found: 212.0708.

3.14 | 2-(4-(benzyl-oxy)phenyl)benzoxazole (1m)[5e]

Elute solution (hexane:EtOAc=5:1 with 5% NEt_3); yield 66%; white solid; mp=149~150°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=8.22 (d, *J*=8.4 Hz, 2H), 7.79-7.73 (m, 1H), 7.60-7.54 (m, 1H), 7.50-7.31 (m, 7H), 7.12 (d, *J*=8.7 Hz, 2H), 5.16 (s, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=163.3, 161.6, 150.8, 142.4, 136.5, 129.6, 128.9, 128.4, 127.7, 124.8, 124.6, 120.1, 119.8, 115.4, 110.6, 70.3 ppm. IR (KBr): 3047, 2930, 2913, 2857, 1617, 1600, 1577, 1497, 1451, 1248, 1172, 1057, 1010, 831, 744, 697, 523 cm^{-1}. LRMS (ESI): $C_{20}H_{15}NO_2$, *m/z*=302 for $[M+H]^+$. HRMS (ESI): $C_{20}H_{15}NO_2$, *m/z* calcd. for $[M+H]^+$: 302.1176; found: 302.1175.

3.15 | 4-(benzoxazol-2-yl)-N,N-di-methyl-aniline (1n)[7e]

Elute solution (hexane:EtOAc=5:1 with 5% NEt_3); yield 34%; brown solid; mp=177~179°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=8.11 (d, *J*=8.7 Hz, 2H), 7.72-7.67 (m, 1H), 7.54-7.49 (m, 1H), 7.32-7.24 (m, 2H), 6.77 (dt, *J*=9.5, 2.3 Hz, 2H), 3.06 (s, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=164.4, 152.6, 150.8, 142.8, 129.3, 124.3, 124.1, 119.3, 114.4, 111.8, 110.3, 40.3 ppm. IR (KBr): 3048, 2896, 1614, 1566, 1513, 1454, 1373, 1242, 1180, 1055, 917, 811, 747, 509 cm^{-1}. LRMS (ESI): $C_{15}H_{14}N_2O$, *m/z*=239 for $[M+H]^+$. HRMS (ESI): $C_{15}H_{14}N_2O$, *m/z* calcd. for $[M+H]^+$: 239.1179; found: 239.1178.

3.16 | 2-(pyridin-4-yl)benzoxazole (1o)[7i]

Elute solution (hexane:EtOAc=5:1 with 5% NEt_3); yield 42%; white solid; mp=128~129°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=7.78 (dd, *J*=4.5, 1.5 Hz, 2H), 8.03 (dd, *J*=4.8, 1.5 Hz, 2H), 7.81-7.75 (m, 1H), 7.61-7.55 (m, 1H), 7.43-7.32 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=160.6, 150.9, 150.8, 141.8, 134.4, 126.4, 125.2, 121.0, 120.7, 111.0 ppm. IR (KBr): 3042, 1614, 1594, 1538, 1469, 1449, 1410, 1345, 1292, 1225, 1110, 1055, 926, 831, 750, 703, 515 cm^{-1}.

LRMS (ESI): $C_{12}H_8N_2O$, *m/z*=197 for $[M+H]^+$. HRMS (ESI): $C_{12}H_8N_2O$, *m/z* calcd. for $[M+H]^+$: 197.0709; found: 197.0710.

3.17 | 2-cyclohexyl-benzoxazole (1p)[4d]

Elute solution (hexane:EtOAc=5:1 with 5% NEt_3); yield 67%; yellow solid; mp=36~37°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=7.65-7.57 (m, 1H), 7.40-7.33 (m, 1H), 7.20-7.15 (m, 2H), 2.93-2.77 (m, 1H), 2.15-2.02 (m, 2H), 1.82-1.56 (m, 5H), 1.42-1.22 (m, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=170.6, 150.8, 141.5, 124.5, 123.1, 119.8, 110.4, 38.0, 30.6, 25.9, 25.8 ppm. IR (KBr): 3053, 2930, 2852, 1611, 1566, 1455, 1241, 1155, 1010, 940, 834, 764, 741 cm^{-1}. LRMS (ESI): $C_{13}H_{15}NO$, *m/z*=202 for $[M+H]^+$. HRMS (ESI): $C_{13}H_{15}NO$, *m/z* calcd. for $[M+H]^+$: 202.1226; found: 202.1228.

3.18 | 2-(furan-2-yl)benzoxazole (1q)[7e]

Elute solution (hexane:EtOAc=10:1 with 5% NEt_3); yield 22%; red brown solid; mp=83~85°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=7.77-7.72 (m, 1H), 7.65 (m, 1H), 7.57-7.52 (m, 1H), 7.36-7.31 (m, 2H), 7.26 (d, *J*=3.8 Hz, 1H), 6.60 (m, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=155.5, 150.3, 145.9, 142.8, 141.8, 125.5, 125.0, 120.3, 114.5, 112.4, 110.7 ppm. IR (KBr): 3126, 3109, 3064, 1645, 1634, 1620, 1589, 1536, 1474, 1449, 1396, 1343, 1301, 1245, 1158, 1080, 1013, 940, 901, 884, 794, 758, 744, 590, 431 cm^{-1}. LRMS (ESI): $C_{11}H_7NO_2$, *m/z*=186 for $[M+H]^+$. HRMS (ESI): $C_{11}H_7NO_2$, *m/z* calcd. for $[M+H]^+$: 186.0550; found: 186.0550.

3.19 | 2-(thiophen-2-yl)benzoxazole (1r)[7e]

Elute solution (hexane:EtOAc=5:1 with 5% NEt_3); yield 58%; yellow solid; mp=94~96°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=7.89 (dd, *J*=3.9, 1.2 Hz, 1H), 7.76-7.71 (m, 1H), 7.55-7.49 (m, 2H), 7.35-7.29 (m, 2H), 7.15 (t, *J*=4.4 Hz, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=159.1, 150.5, 142.1, 130.3, 130.0, 129.7, 128.3, 125.2, 124.8, 119.9, 110.5 ppm. IR (KBr): 3081, 1614, 1569, 1494, 1452, 1421, 1245, 1225, 1049, 1004, 850, 792, 758, 741, 716 cm^{-1}. LRMS (ESI): $C_{11}H_7NOS$, *m/z*=202 for $[M+H]^+$. HRMS (ESI): $C_{11}H_7NOS$, *m/z* calcd. for $[M+H]^+$: 202.0321; found: 202.0323.

3.20 | 2-(thiophen-3-yl)benzoxazole (1s)[7e]

Elute solution (hexane:EtOAc=5:1 with 5% NEt_3); yield 89%; white solid; mp=132~134°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=8.18 (s, 1H), 7.79 (d, *J*=5.1 Hz, 1H), 7.77-7.73 (m, 1H), 7.56-7.51 (m, 1H), 7.45-7.40 (m, 1H), 7.35-7.31 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=159.8, 150.5, 142.1, 129.4, 128.2, 127.1, 126.7, 125.1, 124.7, 120.0, 110.6 ppm. IR (KBr): 3092, 1620, 1580, 1494, 1452, 1407, 1278, 1242, 1055, 1001, 940, 864, 800, 758, 744, 719, 601 cm^{-1}. LRMS (ESI): $C_{11}H_7NOS$, *m/z*=202 for $[M+H]^+$. HRMS (ESI): $C_{11}H_7NOS$, *m/z* calcd. for $[M+H]^+$: 202.0321; found: 202.0323.

3.21 | 2-(1H-pyrrol-2-yl)benzoxazole (1t)

Elute solution (hexane:EtOAc=5:1 with 5% NEt_3); yield 31%; white solid; mp=144~145°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=11.64 (bs, 1H), 7.73-7.65 (m, 1H), 7.61-7.53 (m, 1H), 7.39-7.29 (m, 2H), 7.19-7.13 (m, 1H), 7.10-7.04 (m, 1H), 6.45-6.37 (m, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=158.8, 150.3, 141.7, 124.8, 124.5, 123.6, 119.8, 118.7, 113.7, 110.9, 110.6 ppm. IR (KBr): 3171, 3137, 3020, 1630, 1614, 1586, 1572, 1555, 1536, 1519, 1504, 1455, 1401, 1241, 1127, 1032, 948, 730, 666, 430 cm^{-1}. LRMS (ESI): $C_{11}H_8N_2O$, *m/z*=185 for $[M+H]^+$. HRMS (ESI): $C_{11}H_8N_2O$, *m/z* calcd. for $[M+H]^+$: 185.0709; found: 185.0709.

3.22 | 2-(benzylideneamino)phenol (2a)[13]

Under argon, 2-aminophenol (2.0005 g, 0.0181 mol) and $MgSO_4$ (7.2955 g, 0.0605mol) were dissolved in anhydrous THF or CH_2Cl_2 (20 mL) before benzaldehyde (2.4 mL, 0.0234 mol) was added to the solution. Aft stirred at room temperature for overnight, the reaction was filtered, washed by EtOAc and concentrated. The crude product was purified through a pad of silica gel twice using hexane:EtOAc=10:1 with 10% NEt_3 as elute solution to afford 2a as an red-brown solid (3.4735 g, 0.0176 mol, 97%); mp=88~89°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=8.71 (s, 1H), 7.97-7.91 (m, 2H), 7.55-7.47 (m, 3H), 7.32 (dd, *J*=8.1, 1.5 Hz, 1H), 7.22 (td, *J*=7.7, 1.5 Hz, 1H), 7.05 (dd, *J*=8.1, 1.5 Hz, 1H), 6.93 (td, *J*=7.7, 1.5 Hz, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ=157.3, 152.4, 135.9, 135.6, 131.7, 129.0, 128.9, 120.2, 116.1, 116.1, 115.2 ppm. IR (KBr): 3333, 3036, 3014, 1623, 1583, 1572, 1480, 1449, 1379, 1248, 1147, 1027, 850, 763, 688, 632, 501 cm^{-1}. LRMS (ESI): $C_{13}H_{11}NO$, *m/z*=198 for $[M+H]^+$. HRMS (ESI): $C_{13}H_{11}NO$, *m/z* calcd. for $[M+H]^+$: 198.0913; found: 198.0915.

ACKNOWLEDGMENTS

We thank Ministry of Science and Technology (MOST 105-2113-M-390-004)/(MOST 104-2633-M-390-001) and National Science Council (NSC-102-2113-M-390-002) for the financial support, Prof. Tsengchang Tsai for assistance of research work and Ms. Hsiaoching Yu for the assistance of LRMS and HRMS.

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How to cite this article: Chang W, Sun Y, and Huang Y. One-pot green synthesis of benzoxazole derivatives through molecular sieve-catalyzed oxidative cyclization reaction. *Heteroatom Chem*. 2017;00:e21360. doi:10.1002/hc.21360