

Efficient Aerobic Oxidative Synthesis of 2-Substituted Benzoxazoles, Benzothiazoles, and Benzimidazoles Catalyzed by 4-Methoxy-TEMPO**

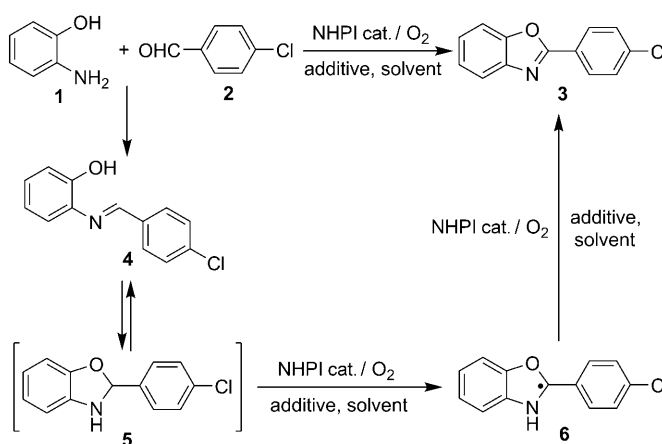
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Aerobic oxygenation/oxidation of hydrocarbons, alcohols, and amines catalyzed by aminoxyl radicals have been extensively studied.^[1] However, its application in the catalytic oxidative synthesis of heterocycles is rare. Herein we report a novel and efficient aerobic approach for the synthesis of 2-substituted benzoxazoles, benzothiazoles, and benzimidazoles by using a one-pot reaction of aldehydes with 2-aminophenol, 2-aminothiophenol, and *o*-phenylenediamine, respectively, and an organic aminoxyl radical as the catalyst.

Five-membered heterocyclic rings, such as benzoxazoles, benzothiazoles, and benzimidazoles, are present in natural products, and in synthetic pharmaceutical and agrochemical compounds.^[2] These compounds have been extensively studied for their biological and therapeutic activities, such as a cathepsin S inhibitor,^[3] a HIV reverse transcriptase inhibitor,^[4] an anticancer agent,^[5] and an orexin-1 receptor antagonist.^[6]

Classical methods for the synthesis of benzoxazoles involve two approaches. One is the copper-catalyzed intramolecular *ortho* arylation of *o*-haloanilides or the intermolecular domino annulations of *o*-arylhalides with acylamides.^[7] The second approach is the condensation of 2-aminophenol with either carboxylic acid derivatives under strong acid/high temperature conditions,^[8] or aldehydes with subsequent oxidation using strong oxidants such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),^[9] PhI(OAc)₂,^[10] Th⁺ClO₄[−],^[11] pyridiniumchlorochromate (PCC),^[12] and BaMnO₄.^[13] Recently, catalytic oxidative reactions using oxygen as the terminal oxidant have received much attention because of their green chemistry and atom economy aspects. The aerobic catalytic synthesis of benzoxazoles promoted by activated carbon^[14] or copper nanoparticles^[15] has recently been reported. However, these reactions require the use of large amounts of the catalyst (50 wt. % of special activated carbon) or excess base, and the yields were not satisfactory. Therefore, a more effective and environmentally friendly process is needed.

Recently, we reported an efficient approach to the oxidative dehydrogenation of Hantzsch dihydropyridines and pyrazolines using *N*-hydroxyphthalimide (NHPI) as the catalyst.^[16] As an extension of this chemistry, we attempted to synthesize 2-aryl benzoxazoles **3** by the aerobic oxidation of Schiff base 2-(4-chlorobenzylideneamino)-phenol (**4**), which was obtained from the condensation of 2-aminophenol (**1**) and aldehyde **2**, using NHPI as the catalyst. The mechanism as shown in Scheme 1 was assumed to be operative.



Scheme 1. A proposed mechanism for the NHPI-catalyzed aerobic oxidative synthesis of 2-aryl benzoxazole.

We supposed that if benzoxazoline **5** was in equilibrium with imine **4**, the former could be easily oxidized to benzoxazole **3** by a hydrogen abstraction from the activated C–H bond of the benzoxazoline. This sequence could be initiated by a phthalimide-*N*-oxyl radical (PINO) generated in situ from the oxidation of NHPI by oxygen. Although several reaction conditions were tried to accomplish this reaction, only one gave target compound benzoxazole **3** albeit in unsatisfactory yield at high temperature using PhCN as the solvent (Table 1, entries 1–10). High temperature and PhCN as the solvent were needed because the cyclization of imine **4** to benzoxazoline **5** was difficult at low temperature. Notably, 4-chlorobenzaldehyde oxime was obtained as a product at relatively low temperature using CH₃CN as the solvent (Table 1, entries 3 and 4). To validate our proposal, *o*-phenylenediamine (**1e**) was used instead of 2-aminophenol (**1**) and the reaction was complete in acetonitrile at 80 °C to give 2-(4-chlorophenyl)-1*H*-benzimidazole in 83 % yield. This yield results from the much higher nucleophilicity of the *ortho*-amine group compared to that of the *ortho*-hydroxy group for the cyclization to the imine.

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[**] We are grateful to the National Natural Science Foundation of China (Grant No. 20472027) for financial support. We also thank Dr. Wei Yu for helpful discussions. TEMPO = 2,2,6,6-tetramethyl-1-piperidin-1-oxyl free radical.

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Table 1: Effect of aminoxyl radicals on the oxidative synthesis of 2-aryl benzoxazole.^[a]

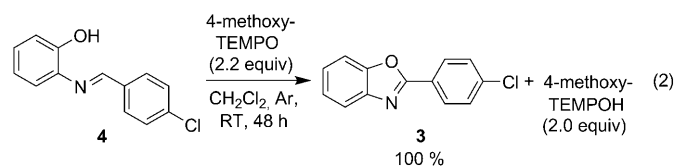
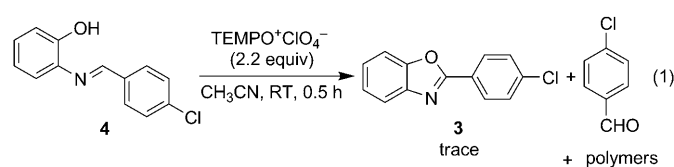
Entry	Catalyst [mol %]	Solvent	T [°C]	Yield [%] ^[b]
1	NHPI (10)	CH ₃ CN	80	0
2 ^[c]	NHPI/Co(OAc) ₂ (10/0.5)	CH ₃ CN	RT	0
3	NHPI/Co(OAc) ₂ (10/0.5)	CH ₃ CN	80	0 ^[d]
4	NHPI (100)	CH ₃ CN	80	0 ^[d]
5	NHPI (10)	CH ₃ CO ₂ C ₂ H ₅	80	0
6	NHPI (10)	CH ₃ CO ₂ C ₄ H _{9-n}	120	0
7	NHPI (10)	CH ₃ CH ₂ OH	80	0
8	NHPI (10)	PhCN	120	trace
9	NHPI (10)	PhCN	150	15
10 ^[e]	NHPI (10)	PhCN	150	71
11	TEMPO (5)	CH ₃ CN	80	18
12 ^[c]	TEMPO/CuBr (5/0.5)	CH ₃ CN	RT	trace
13 ^[c]	TEMPO/CuBr (10/1)	CH ₃ CN	RT	trace
14	TEMPO (5)	CH ₃ CO ₂ C ₂ H ₅	80	13
15	TEMPO (5)	CH ₃ CO ₂ C ₄ H _{9-n}	120	23
16	TEMPO (10)	CH ₃ CH ₂ OH	80	15
17	TEMPO (5)	Benzene	80	21
18	TEMPO (5)	toluene	110	43
19 ^[f]	TEMPO (10)	xylenes ^[g]	120	95
20	TEMPO (5)	xylenes ^[g]	120	95
21 ^[e]	TEMPO (1)	xylenes ^[g]	120	96
22	TEMPO (5)	xylenes ^[g]	RT	5
23	0	xylenes ^[g]	120	0

[a] 2-aminophenol (**1**; 1 mmol) and aldehyde **2** (1 mmol) were dissolved in solvent (3 mL) in a 25 mL three-necked flask and stirred for 1 h at different temperatures. The catalyst was then added and the mixture stirred under an oxygen atmosphere for another 5 h. [b] ¹H NMR analysis. [c] Used 1 mol of Schiff base **4** as the substrate. [d] 4-Chlorobenzaldehyde oxime was obtained as the product. [e] After 15 h. [f] After 2.5 h. [g] Mixture of *o*-, *m*-, and *p*-xylene.

Next, we turned our attention to another aminoxyl radical, 4-methoxy-2,2,6,6-tetramethyl-1-piperidinyloxy (4-methoxy-TEMPO) free radical, which is widely used for the selective oxidation of primary or secondary alcohols.^[1c-d,17] We initially used stoichiometric amounts of TEMPO⁺ClO₄⁻ as the oxidant to perform this reaction. However, the starting material, 2-hydroxy-bezoimine **4**, was oxidatively decomposed to the corresponding aldehyde and 2-aminophenol (**1**); the strong oxidizing ability of TEMPO⁺ caused the latter to be oxidized to give polymers, so only a trace amount of benzoxazole **3** was observed. However, when a stoichiometric amount of 4-methoxy-TEMPO radical was used as the oxidant instead of TEMPO⁺, target molecule benzoxazole **3** was produced quantitatively in 48 hours at room temperature, indicating that 4-methoxy-TEMPO radical is a privileged oxidant in the oxidative dehydrogenation of Schiff base **4** [Eq. (1) and Eq. (2)].

4-methoxy-TEMPOH can be slowly oxidized to 4-methoxy-TEMPO radical in air at room temperature, so a strategy for the aerobic catalytic oxidative synthesis of benzoxazole using 4-methoxy-TEMPO radical as the catalyst was developed.

To optimize the reaction conditions we used various solvents and discovered that nonpolar aromatic solvents gave



higher yields than polar solvents under the same reaction conditions; the solvent polarity affects the stability of the resonance structure of 4-methoxy-TEMPO radical and is also responsible for its reactivity with the substrate^[18] (Table 1, entries 11, 14, 16, and 17). In addition, temperature significantly affected the reaction; high temperatures accelerated the rate of the hydrogen abstraction between 4-methoxy-TEMPO radical and the substrate, and the rate at which 4-methoxy-TEMPO radical was regenerated (Table 1, entries 17–19 and 22). Finally, we found that 4-methoxy-TEMPO/xylene catalytic system is best. All the conditions we optimized are listed in entries 11–23 in Table 1.

Notably, if 1 mol % of 4-methoxy-TEMPO was used, the reaction was complete in 15 hours, resulting in benzoxazole **3** in 96% yield. We checked the turnover number (TON) and turnover frequency (TOF) values for different amounts of 4-methoxy-TEMPO radical (Table 2). The use of 1 mol % of 4-methoxy-TEMPO radical gave the best TON and TOF values.

The use of 5 mol % of 4-methoxy-TEMPO radical in the following reactions was aimed at reducing the reaction times. A variety of 2-aminophenol derivatives (**1a–1c**) and aldehydes **2** were used in this oxidative cyclization by the in situ formation of Schiff bases, leading to the synthesis of 2-substituted benzoxazoles (**3a–3o**; Table 3).

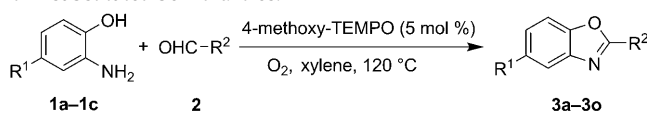
Aryl aldehydes gave excellent yields of 2-aryl benzoxazoles, and aliphatic aldehydes participated in the reaction to give the corresponding 2-alkyl benzoxazoles in good yields. When heptylaldehyde was used in the reaction, two benzoxazoles, **3i** and **3j**, were obtained in 20% and 35% yields, respectively (based on 2-aminophenol; Table 3, entry 9). We believe that 4-methoxy-TEMPO radical initially interacts with 2-hydroxybenzoimine^[19] and initiates the reaction with a hydrogen abstraction from the O–H bond of the phenol moiety^[20] to produce phenoxyl radical **7** and 4-methoxy-

Table 2: TON and TOF values for 4-methoxy-TEMPO radical catalyzed oxidative synthesis of 2-aryl benzoxazole.^[a]

Entry	4-methoxy-TEMPO [mol %]	t [h]	TON	TOF [h ⁻¹]
1	10	2.5	10	4
2	5	5	20	4
3	1	15	100	6.7

[a] Calculated values based on Table 1, entries 19–21.

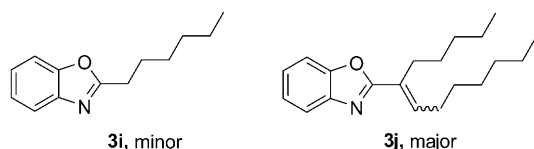
Table 3: 4-methoxy-TEMPO radical catalyzed aerobic oxidative synthesis of 2-substituted benzoxazoles.^[a]



Entry	R ¹	R ²	t [h]	Yield [%] ^[b]
1	H (1a)	4-ClC ₆ H ₄	5	95 (3a)
2	H (1a)	Ph	5	90 (3b)
3	H (1a)	4-NO ₂ C ₆ H ₄	6	91 ^[c] (3c)
4	H (1a)	2-CH ₃ C ₆ H ₄	5	96 (3d)
5	H (1a)	4-CH ₃ OC ₆ H ₄	4	95 (3e)
6	H (1a)	E-C ₆ H ₅ CH=CH	9	82 (3f)
7	H (1a)	2-furyl	8	88 (3g)
8	H (1a)	(CH ₃) ₃ C	1	88 (3h)
9	H (1a)	CH ₃ (CH ₂) ₅	3	20, 35 ^[d] (3i,j)
10	Cl (1b)	4-CH ₃ OC ₆ H ₄	13	95 (3k)
11	Cl (1b)	4-NO ₂ C ₆ H ₄	10	92 ^[c] (3l)
12	NO ₂ (1c)	2-CH ₃ C ₆ H ₄	11	93 ^[c] (3m)
13	NO ₂ (1c)	4-ClC ₆ H ₄	17	93 ^[c] (3n)
14	NO ₂ (1c)	(CH ₃) ₃ C	6	91 ^[c] (3o)

[a] 2-aminophenol (5 mmol), aldehyde (5 mmol) and xylenes (15 mL; mixture of *o*-, *m*-, and *p*-xylene) was placed in a 100 mL three-necked flask and stirred at 120 °C for 0.5 h. 4-methoxy-TEMPO radical (5 mol %; 47 mg, 0.25 mmol) was then added to the mixture and stirred for several hours under an oxygen atmosphere. [b] Yield of isolated product obtained after purification by silica gel column chromatography unless noted otherwise. [c] Yield of isolated product obtained after recrystallization. [d] Two compounds were obtained and structures are shown below.

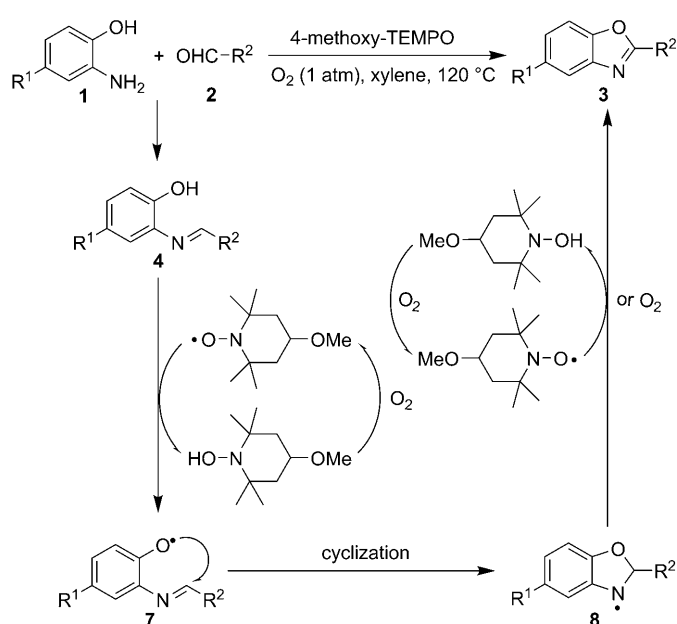
TEMPOH which can be reoxidized to 4-methoxy-TEMPO radical by oxygen. Phenoxyl radical **7** is additionally stabilized



by the imine moiety and then undergoes intramolecular 5-endo cycloaddition to the imine to form the corresponding aminyl radical **8**. The driving force for aromatization renders the second hydrogen abstraction, between the aminyl radical **8** and 4-methoxy-TEMPO/or oxygen, very effective and eventually yield target compound benzoxazole **3**. A proposed catalytic cycle is shown in Scheme 2.

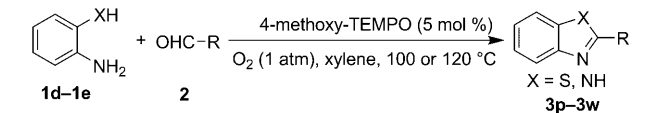
Having successfully achieved the aerobic oxidative synthesis of benzoxazoles, we expanded the catalytic system to the oxidative synthesis of benzothiazoles and benzimidazoles using 2-amino-thiophenol (**1d**) or *o*-phenylenediamine (**1e**) respectively with aldehydes as starting materials. As shown in Table 4, benzothiazoles and benzimidazoles were produced in high yields.

In conclusion, the reaction of 4-methoxy-TEMPO radical with 2-benzylideneaminophenols provides a novel and efficient approach for the aerobic catalytic oxidative synthesis of various heterocycles. The 2-substituted benzoxazoles, benzo-



Scheme 2. A proposed mechanism for 4-methoxy-TEMPO-catalyzed aerobic oxidative synthesis of 2-substituted benzoxazoles.

Table 4: 4-methoxy-TEMPO radical catalyzed aerobic oxidative synthesis of 2-substituted benzothiazoles and benzimidazoles.^[a]



Entry	X	R	t [h]	Yield [%] ^[b]
1	S (1d)	Ph	9	80 (3p)
2	S (1d)	4-ClC ₆ H ₄	11	85 (3q)
3	S (1d)	4-NO ₂ C ₆ H ₄	7	87 ^[d] (3r)
4	S (1d)	(CH ₃) ₃ C	3	77 (3s)
5 ^[c]	NH (1e)	Ph	11	91 ^[d] (3t)
6 ^[c]	NH (1e)	4-ClC ₆ H ₄	10	91 ^[d] (3u)
7 ^[c]	NH (1e)	4-CH ₃ OC ₆ H ₄	7	89 ^[d] (3v)
8 ^[c]	NH (1e)	2-Furyl	13	90 ^[d] (3w)

[a] 2-aminothiophenol or *o*-phenylenediamine (5 mmol), aldehydes (5 mmol), and xylenes (15 mL; mixture of *o*-, *m*-, and *p*-xylene) was placed in a 100 mL three-necked flask and stirred at 100 °C for 0.5 h. 4-methoxy-TEMPO radical (5 mol %; 47 mg, 0.25 mmol) was added to the mixture which was then stirred for several hours under an oxygen atmosphere. [b] Yield of isolated product after purification by silica gel column chromatography unless noted otherwise. [c] At 120 °C. [d] Yield of isolated product obtained by recrystallization.

thiazoles, and benzimidazoles can be obtained by using a one-pot reaction of aldehydes with 2-aminophenol, 2-aminothiophenol and *o*-phenylenediamine, respectively, with 4-methoxy-TEMPO radical as the catalyst. The extension of this catalytic system for the preparation of other useful heterocycles is underway in our laboratory.

Experimental Section

Aerobic synthesis of benzoxazole **3a** (Table 3, entry 1): 2-aminophenol (546 mg, 5 mmol) and 4-chlorobenzaldehyde (703 mg,

5 mmol) were placed in a 100 mL three-necked flask containing xylenes (15 mL; mixture of *m*-, *o*-, and *p*-xylene). The reaction mixture was heated to 120°C for 0.5 h with stirring. 4-methoxy-TEMPO (47 mg, 5 mol %) was then added to the mixture which was then stirred under an oxygen atmosphere for 5 h. When the starting materials were completely consumed as determined by TLC analysis, the reaction mixture was concentrated under vacuum and the product was isolated after purification using silica gel column chromatography as a white crystalline solid (1.100 g; 95 %). The identity and purity of the product was confirmed by ¹H and ¹³C NMR spectroscopic analysis.

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