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ORIGINAL PAPER

Aerobic oxidative synthesis of 2-arylbenzimidazoles, 2-arylbenzoxazoles, and 2-arylbenzothiazoles from arylmethanols or arylmethylamines catalyzed by Fe(III)/TEMPO under solvent-free conditions

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Abstract A simple and efficient aerobic oxidative synthesis of 2-arylbenzimidazoles, 2-arylbenzoxazoles, and 2-arylbenzothiazoles from arylmethanols or arylmethylamines with *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol catalyzed by $Fe_2(SO_4)_3$/TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) system under solvent-free conditions. This reaction uses air as an environmental and economic oxidant, tolerates a variety of functional groups on the aromatic ring of the benzylic partner, and affords the products in moderate yields.

Keywords 2-arylbenzimidazoles · 2-arylbenzoxazoles · 2-arylbenzothiazoles iron TEMPO

Introduction

Five-membered N-containing heteroaromatic compounds are important structures found in natural and synthetic compounds. Among them, benzimidazole and its derivatives are crucial core structures which exhibit significant pharmacological and biological activities, such as anticonvulsant, anticancer, antiulcer, antihypertensive, antibacterial, and antihistaminic agents. [1–9].

They also have been applied in dyes, fluorescence, chemosensing, and corrosion science [10–14] In addition, they are very useful intermediates/subunits in organic reactions [15, 16]. The excellent characteristics of benzimidazole derivatives have promoted extensive studies for their synthesis. Typically, there are two methods for the synthesis of benzimidazoles. One is the coupling of *o*-phenylenediamine with carboxylic acids or their derivatives (nitriles, imidates, and orthoesters) under harsh dehydrating conditions, such as strong acidic conditions, high temperature conditions [17–33]. The other is oxidative cyclization of aniline Schiff bases promoted by oxidants, in which benzimidazoles are often generated from the condensation of *o*-phenylenediamine and aldehydes [34–41] However, this method has some drawbacks such as requiring a stoichiometric amount of oxidant, generating environmentally hazardous/toxic by-products, and using malodorous and unstable aldehydes. Besides, different methods for the direct synthesis of benzimidazoles, benzoxazoles, and benzothiazoles and also recent published papers for the preparation of benzimidazoles catalyzed by transition metal and biocatalyst had also recently reported [42–47].

In recent years, the preparation of benzimidazoles have been greatly improved, especially by employing the reaction of *o*-phenylenediamine with the greener, cheaper, and more available alcohols or amines, but drawbacks still remain, for example, the former methods require complex and expensive metal catalysts, a large excess of oxidants, which also produces large amounts of undesired waste, and an inert atmosphere [48–50] Many issues have yet to be satisfactorily addressed. So, the development of new efficient and greener methods for their synthesis is, therefore, highly desirable.

Recently, the aerobic oxidative reactions have attracted increasing attention, which are comparatively green, preferable, and practical processes, due to the use of pure oxygen or air as the economic and green oxidant, much more easily disposable catalysts, and milder reaction conditions, along with generating water as the by-product. However, most reactions still require special conditions, expensive

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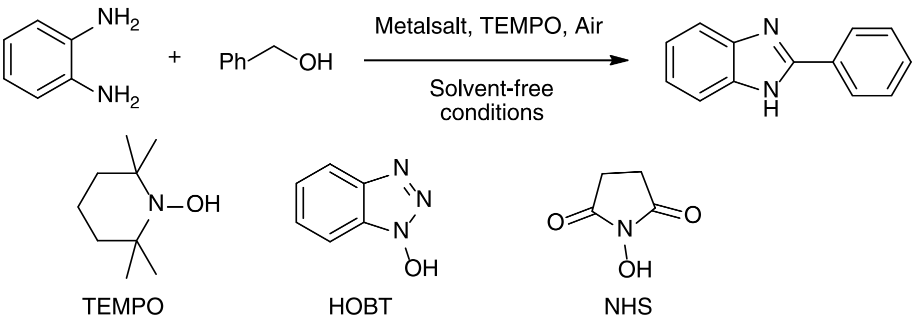
Table 1 Condition optimization for aerobic oxidation of *o*-phenylenediamine and benzyl alcohol



Entry	Benzyl alcohol (equiv.)	Metal salt (mol %)	Catalyst (mol %)	Oxidant	Solvent	Temp. (°C)	Reaction time (h)	Yield[a] (%)
1	1.2	$Fe_2(SO_4)_3$ (0)	–	Air	–	80	24	Trace
2	1.2	$Fe_2(SO_4)_3$ (10)	–	Air	–	80	24	35
3	1.2	$Fe_2(SO_4)_3$ (0)	TEMPO (10)	Air	–	80	24	21
4	1.2	$Fe_2(SO_4)_3$ (10)	TEMPO (10)	Air	–	80	24	62
5	1.2	$FeCl_3$ (10)	TEMPO (10)	Air	–	80	24	42
6	1.2	$Fe(NO_3)_3$ (10)	TEMPO (10)	Air	–	80	24	37
7	1.2	CuCl (10)	TEMPO (10)	Air	–	80	24	46
8	1.2	CuI (10)	TEMPO (10)	Air	–	80	24	55
9	1.2	$Cu(OAc)_2$ (10)	TEMPO (10)	Air	–	80	24	42
10	1.2	$Fe_2(SO_4)_3$ (10)	HOBT (10)	Air	–	80	24	57
11	1.2	$Fe_2(SO_4)_3$ (10)	NHS (10)	Air	–	80	24	49
12	1.2	$Fe_2(SO_4)_3$ (10)	TEMPO (10)	Air	DCE	80	24	21
13	1.2	$Fe_2(SO_4)_3$ (10)	TEMPO (10)	Air	EtOAc	80	24	Trace
14	1.2	$Fe_2(SO_4)_3$ (10)	TEMPO (10)	Air	Dioxane	80	24	54
15	1.2	$Fe_2(SO_4)_3$ (10)	TEMPO (10)	Air	Toluene	80	4	59
16	1.2	$Fe_2(SO_4)_3$ (10)	TEMPO (10)	Air	–	110	24	83
17	1.2	$Fe_2(SO_4)_3$ (10)	TEMPO (10)	Air	–	130	24	83
18	1.5	$Fe_2(SO_4)_3$ (10)	TEMPO (10)	Air	–	110	24	72
19	1	$Fe_2(SO_4)_3$ (10)	TEMPO (10)	Air	–	110	24	69
20	1.2	$Fe_2(SO_4)_3$ (5)	TEMPO (5)	Air	–	110	24	75
21	1.2	$Fe_2(SO_4)_3$ (2.5)	TEMPO (2.5)	Air	–	110	24	43
22[b]	1.2	$Fe_2(SO_4)_3$ (10)	–	H_2O_2	–	50	24	Trace
23[b]	1.2	$Fe_2(SO_4)_3$ (10)	–	Oxone	–	110	24	Trace
24	1.2	$Fe_2(SO_4)_3$ (10)	TEMPO (10)	O_2	–	110	24	83
25	1.2	$Fe_2(SO_4)_3$ (10)	TEMPO (10)	N_2	–	110	24	Trace

Reaction conditions a mixture of *o*-phenylenediamine and benzyl alcohol, Metal salt, TEMPO, was mixed in a 10 ml three-necked flask, and then stirred rapidiy for several hours. The reaction progress was monitored by TLC

[a] Isolated yield

[b] The reaction was conducted under N_2 condition

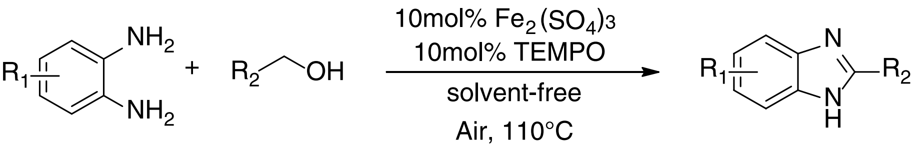
and rare noble metal catalysts, or dangerous pure oxygen as the oxidant [51–54].

Herein, we introduce a simple and efficient method for directly aerobic oxidative synthesis of benzimidazoles, benzoxazoles, and benzothiazoles from the arylmethylamines or the arylmethanols with *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol catalyzed by $Fe_2(SO_4)_3$/TEMPO under solvent-free using air as the oxidant. This method tolerates various functional groups on the aromatic ring of the benzylic partner, and affords the products in moderate yields.

Result and discussion

Initially, *o*-phenylenediamine and benzyl alcohol were selected as a model substrate to optimize the reaction conditions (Table 1). When the model reaction was carried

Table 2 Synthesis of 2-substituted benzimidazoles from the arylmethanol and *o*-phenylenediamines



Entry	R_1	R_2	Reaction time (h)	Yield (%)[a]
1	H	C_6H_5	24	83
2	H	4-BrC_6H_4	24	85
3	H	4-ClC_6H_4	24	85
4	H	2-ClC_6H_4	26	81
5	H	2, 4-ClC_6H_3	24	80
6	H	4-$NO_2C_6H_4$	20	86
7	H	4-$MeOC_6H_4$	26	83
8	H	4-$Me_2NC_6H_4$	26	76
9	H	3,4,5-$MeOC_6H_2$	26	80
10	H	2-Furyl	27	73
11	H	5-methyl-2-furyl	28	71
12	H	Pyridin-2-yl	30	69
13	Cl	C_6H_5	26	87
14	4-NO_2	C_6H_5	28	78

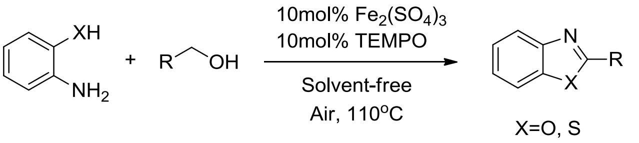
Reaction conditions a mixture of 5 mmol *o*-phenylenediamine and 6 mmol aromatic alcohol, 10 mol % $Fe_2(SO_4)_3$, 10 mol % TEMPO were mixed in a 10 ml three-necked flask, and then stirred rapidiy open to air at 110 °C for several hours. The reaction progress was monitored by TLC

[a] Isolated yield

out under solvent-free conditions, at 80 °C for 24 h, and in the absence of $Fe_2(SO_4)_3$ and TEMPO, traces only of the desire product was obtained (entry 1). In the presence of $Fe_2(SO_4)_3$ alone (entry 2) or of TEMPO alone (entry 3), the yield of 2-phenylbenzimidazole was also very low. We were pleased to find that the combination of $Fe_2(SO_4)_3$ and TEMPO could greatly enhance the yield of the product (entry 4). This indicated that both $Fe_2(SO_4)_3$ and TEMPO were essential in this reaction. Several other iron and copper salts [$FeCl_3$, $Fe(NO_3)_3$, CuCl, CuI, $Cu(OAc)_2$] were also examined (entries 5–9) and $Fe_2(SO_4)_3$ was found to be the best (entry 4). HOBT (*N*-hydroxybenzotrizole), NHS (*N*-hydroxysuccinimide) were used as catalyst in this reaction, and found that TEMPO was the best choice (entries 4, 10, 11). Solvent screening showed that the reaction under solvent-free conditions gave a higher yield than using solvents (entries 4, 12–15), and the reaction may be the substrates is easier to contact the O_2 in the air than in the solvent. Moreover, $Fe_2(SO_4)_3$ has a poor solubility in organic solvent. The yield was improved by increasing the temperature from 80 °C (entry 4) to 110 °C (entry 16) but remained the same upon further increase of the temperature to 130 °C (entry 17). Thus, 110 °C was selected as the best temperature. The use of 1.2 equivalent of benzyl alcohol gave the best results (compare entry 16 with entries 18–19). Further optimization showed that the optimum amount of $Fe_2(SO_4)_3$ and TEMPO was 10 mol % of each (compare entry 16 with entries 20–21). Besides, hydrogen peroxide and oxone were used instead of air as oxidant for this reaction, the yields were trace (entries 22–23). Finally, we also tested the influence of the gas, lower yield was obtained when the reaction was conducted under N_2, and we found that the O_2 is significant for the reaction. However, using O_2 in the reaction, the yield was equal to use air (entries 16, 24–25). As economic consideration, we chose air as the oxidant. Therefore, the optimal reaction conditions for the synthesis of benzimidazole consist of 10 mol % $Fe_2(SO_4)_3$ and 10 mol % TEMPO as catalyst at 110 °C under solvent-free conditions.

Encouraged by these results, the optimized conditions were then applied to various benzyl (heterocyclic) alcohol and *o*-phenylenediamine to extend the scope of the method. As shown in Table 2, benzyl alcohols bearing electron-donating substituents as well as electron-withdrawing substituents at the *para*-position gave similar yields of 2-arylbenzimidazole (83–86 %, entries 2, 3, 6, 7) as the parent benzyl alcohol (83 %, entry 1). The yield was slightly lower with the substituent in the ortho position (80–81 %, entries 4 and 5). That may be due, in part, to steric hindrance. A lower yield was obtained in the case of the strongly electron-donating para *N*, *N*-dimethylamino substituent (76 %, entry 8). However, three electron-donating methoxy groups, two in the ortho and one in the para-position, did not cause a significant lowering of the yield (80 %, entry 9). Moreover, heteroarylmethanols were also tested in this reaction system, and the yields were moderate (entries 10–12). In addition, 4-chloro-*o*-phenylenediamine and 4-nitro-*o*-phenylenediamine was also employed in the reaction, and to our delight, it resulted in moderate yields (entry 13–14).

Table 3 $Fe_2(SO_4)_3$/TEMPO catalyzed aerobic oxidative synthesis of benzoxazoles and benzothiazoles



Entry	X	R	Reaction time (h)	Yield (%)^a
1	O	Ph	26	85
2	O	4-ClC_6H_4	24	88
3	O	4-$CH_3OC_6H_4$	28	85
4	S	Ph	30	76
5	S	4-ClC_6H_4	28	79
6	S	4-$NO_2C_6H_4$	26	81

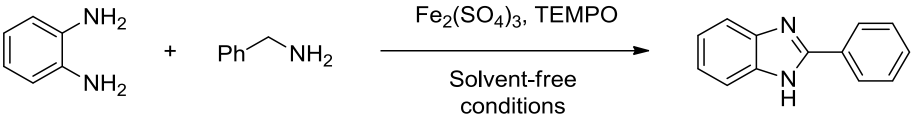
Reaction conditions a mixture of 5 mmol 2-aminophenol or 2-aminothiophenol and 6 mmol aromatic alcohol, 10 mol % $Fe_2(SO_4)_3$, 10 mol % TEMPO were mixed in a 10 ml three-necked flask, and then stirred rapidiy open to air at 110 °C for several hours. The reaction progress was monitored by TLC

[a] Isolated yield

Having successfully achieved the aerobic oxidative synthesis of benzimidazoles, the $Fe_2(SO_4)_3$/TEMPO system was expanded to catalyze the synthesis of benzoxazoles and benzothiazoles using *o*-aminophenol and *o*-aminothiophenol with the arylmethanols, respectively. As summarized in Table 3, *o*-aminophenol and *o*-aminothiophenol were also converted to corresponding benzoxazoles and benzothiazoles in high yields.

The similar method could also be applied to synthesize benzimidazoles through the reactions of arylmethylamines and *o*-phenylenediamine. We began our investigation using *o*-phenylenediamine and benzyl amine as the model substrate under solvent-free conditions at 110 °C for 24 h (Table 4). As expected, the yield of the desired product was very poor in the absence of $Fe_2(SO_4)_3$ and TEMPO (entry 1). Then we use $Fe_2(SO_4)_3$ or TEMPO alone, the results were not satisfying (entries 2 and 3). However, when the model reaction was catalyzed by $Fe_2(SO_4)_3$ and TEMPO, to our delight, the yield was the highest (entry 4). The loading

Table 4 Optimization of the reaction conditions

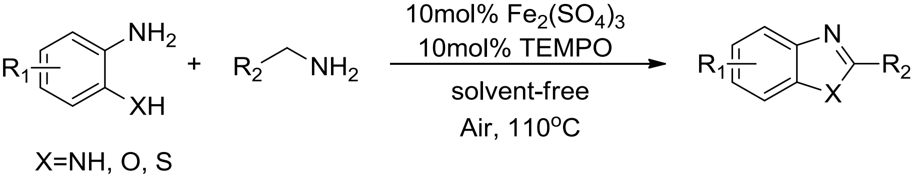


Entry	Benzyl amine (equiv.)	$Fe_2(SO_4)_3$ (mol %)	TEMPO (mol %)	Temp. (°C)	Solvent	Reaction time (h)	Gas	Yield (%)^a
1	0.8	–	–	110	–	24	Air	19
2	0.8	10	–	110	–	24	Air	52
3	0.8	–	10	110	–	24	Air	36
4	0.8	10	10	110	–	24	Air	79
5	1	10	10	110	–	24	Air	82
6	1.2	10	10	110	–	24	Air	88
7	1.5	10	10	110	–	24	Air	81
8	1.2	10	10	80	–	24	Air	77
9	1.2	10	10	100	–	24	Air	83
10	1.2	10	10	130	–	24	Air	87
11	1.2	10	10	110	DCE	24	Air	35
12	1.2	10	10	110	EtOAc	24	Air	12
13	1.2	10	10	110	Dioxane	24	Air	79
14	1.2	10	10	110	Toluene	24	Air	85
11	1.2	10	10	110	–	24	O_2	88
12	1.2	10	10	110	–	24	N_2	Trace

Reaction conditions a mixture of *o*-phenylenediamine and benzyl amine, $Fe_2(SO_4)_3$, TEMPO, were mixed in a 10 ml three-necked flask, and then stirred rapidiy for several hours. The reaction progress was monitored by TLC

[a] Isolated yield

Table 5 $Fe_2(SO_4)_3$/TEMPO catalyzed aerobic oxidation synthesis of 2-substituted benzimidazoles, benzoxazoles, and benzothiazoles from the arylmethylamine and *o*-phenylenediamines, 2-aminophenol or 2-aminothiophenol under air



Entry	X	R_1	R_2	Reaction time (h)	Yield (%)[a]
1	NH	H	C_6H_5	24	88
2	NH	H	4-BrC_6H_4	24	85
3	NH	H	4-ClC_6H_4	24	86
4	NH	H	2-ClC_6H_4	26	84
5	NH	H	2, 4-ClC_6H_3	24	85
6	NH	H	4-$NO_2C_6H_4$	20	90
7	NH	H	4-$MeOC_6H_4$	26	85
8	NH	H	4-$Me_2NC_6H_4$	26	78
9	NH	H	3,4,5-$MeOC_6H_2$	26	83
10	NH	H	2-Furyl	27	80
11	NH	H	5-methyl-2-furyl	28	81
12	NH	H	Pyridin-2-yl	30	69
13	NH	Cl	C_6H_5	28	91
14	NH	4-NO_2	C_6H_5	30	79
15	O	H	C_6H_5	22	90
16	O	H	4-ClC_6H_4	20	89
17	O	H	4-$CH_3OC_6H_4$	24	87
18	S	H	C_6H_5	26	85
19	S	H	4-ClC_6H_4	26	79
20	S	H	4-$NO_2C_6H_4$	24	83

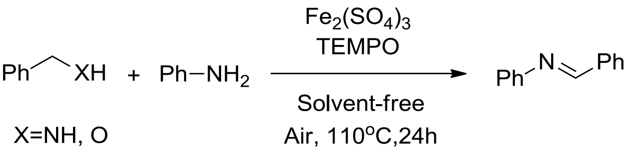
Reaction conditions a mixture of 5 mmol *o*-phenylenediamine, 2-aminophenol or 2-aminothiophenol and 6 mmol aromatic amine, 10 mol % $Fe_2(SO_4)_3$, 10 mol % TEMPO were mixed in a 10 ml three-necked flask, and then stirred rapidiy open to air at 110 °C for several hours. The reaction progress was monitored by TLC

[a] Isolated yield

of benzyl amine screening indicated 1.2 equivalent was the most suitable proportion (entries 4–7). Further condition screening by investigating the effects of reaction temperature, showing that a temperature of 110 °C was optimal (entries 6, 8–10). Furthermore, screening the effects of gas and the results indicated that when the reaction was conducted under N_2, the desired product was trace. We found that the O_2 is significant for the reaction. Moreover, using O_2 in the reaction, the yield was equal to use air (entries 6, 11–12). As economic consideration, we chose air as the oxidant.

To investigate the scope and limitation of this catalytic system, we applied the optimized conditions to different substrates (Table 5). First, *o*-phenylenediamine was chose to react with a series of the benzyl amines bearing electron-donating or electron-withdrawing substituents under the optimized reaction conditions, giving the corresponding products in moderate yields. It seemed that benzyl amines bearing electron-deficient aromatic rings at the *para*-position gave higher yields of products than did those bearing electron-rich aromatic rings (entries 2–9). The reason may that the strong electron-withdrawing groups (NO_2) enhanced the reaction rate. Heteroaryl amines such as *ortho*-furyl methylamine were used in the reaction, and the yields were satisfactory (entries 10–12). In addition, 4-chloro-*o*-phenylenediamine and 4-nitro-*o*-phenylenediamine was also employed in the reaction, the results revealed that the electron-donating group enhanced the reaction, meanwhile electron-withdrawing substituent slowed the reaction (compare entry 1 with entries 13–14). Under the same condition, the methodology was extended to the synthesis of various benzoxazoles and benzothiazoles

Table 6 $Fe_2(SO_4)_3$/TEMPO catalyzed aerobic oxidation of benzylamine and aniline to imine under air

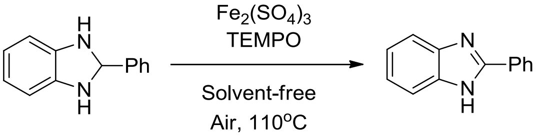


Entry	X	$Fe_2(SO_4)_3$ (mol %)	TEMPO (mol %)	Gas	Yield (%)[a]
1	O	–	–	Air	29
2	O	–	–	N_2	Trace
3	O	10	–	Air	53
4	O	–	10	Air	47
5	O	10	10	Air	89
6	NH	–	–	Air	31
7	NH	–	–	N_2	Trace
8	NH	10	–	Air	59
9	NH	–	10	Air	51
10	NH	10	10	Air	92

Reaction conditions a mixture of 5 mmol aniline and 6 mmol benzylalcohol or benzylamine, $Fe_2(SO_4)_3$, TEMPO were mixed in a 10 ml three-necked flask, and then stirred rapidiy open to air at 110 °C for 24 h

[a] Isolated yield

Table 7 The cyclo-dehydrogenation of benzimidazoline to benzimidazole



Entry	$Fe(NO_3)_3$ (mol %)	TEMPO (mol %)	Oxidant	Yield (%)[a]
1	10	–	Air	39
2	–	10	Air	78
3	10	10	Air	97
4	10	10	N_2	23

Reaction conditions a mixture of 4 mmol benzimidazoline, $Fe_2(SO_4)_3$, TEMPO were mixed in a 5 ml three-necked flask, and then stirred rapidiy open to air at 110 °C for 12 h

[a] Isolated yield

from *o*-aminophenol and *o*-aminothiophenol with benzylamines. The results are summarized in Table 5, benzoxazoles and benzothiazoles were resulted in good yields (entries 15–20).

To understand this reaction further, we conducted a series of examples to gain an insight into possible mechanisms by which this reaction may be operating. Firstly, we turn our attention to the reaction of benzyl alcohol or benzyl amine and aniline to synthesize the imines as shown in Table 6. First, we found that the presence of oxygen is required for the reaction to occur. Only a trace amount of imine was obtained when the reaction was conducted under N_2 (compare entries 1 and 2 with entries 5 and 6). Higher yields were obtained when the reaction was catalyzed by $Fe_2(SO_4)_3$ (entries 3 and 8) or TEMPO (entries 4 and 9). When the reaction was catalyzed by both $Fe_2(SO_4)_3$ and TEMPO, the yield of imine was the highest (entries 5 and 10).

By the encouragement of these results, we speculated, in the imine formation step, *o*-phenylenediamine with benzyl alcohol or benzyl amine took place to form imine 3, and then the imine further reacted with another amine group of *o*-phenylenediamine resulting in the formation of benzimidazoline 4. Secondly, the cyclo-dehydrogenation of benzimidazoline step, preliminary studies of the reaction were conducted, the results are shown in Table 7. Benzimidazoline was treated with 10 mol % $Fe_2(SO_4)_3$ and 10 mol % TEMPO at 110 °C under solvent-free conditions for 12 h, the desired 2-phenylbenzimidazole was isolated in 97 % yield. When the reaction was carried out in the absence of $Fe_2(SO_4)_3$ or TEMPO, the yield decreased substantially. Besides, the reaction could not proceeded under N_2. Therefore, $Fe(NO_3)_3$, TEMPO and Air were essential for the reaction (Table 7).

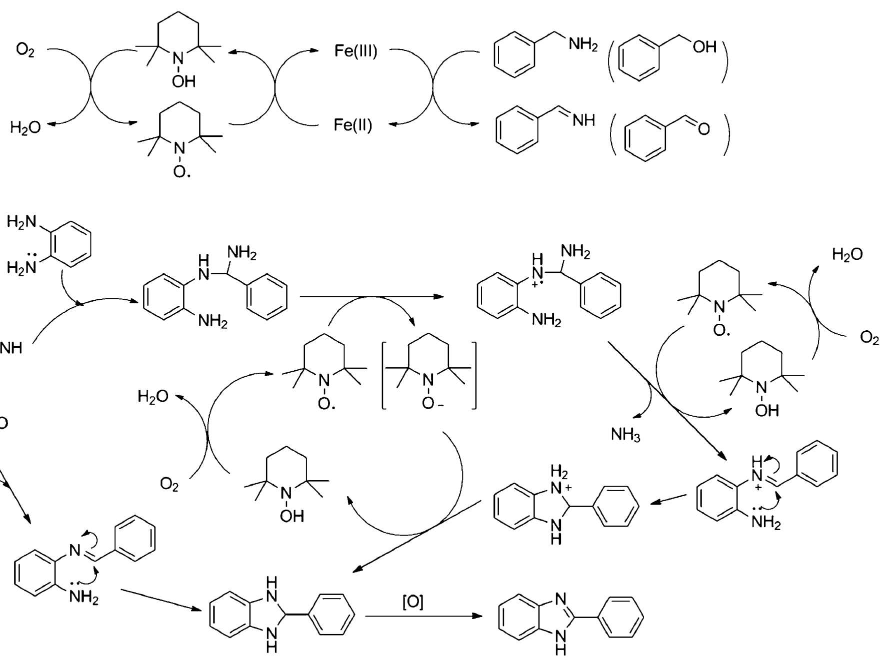
Based on these results and the literature reports [51–55], a proposed pathway for the synthesis of benzimidazoles is shown in Scheme 1. In the benzimidazoline formation step, the aerobic oxidative synthesis imine via the coupling of *o*-phenylenediamine with benzyl alcohol or benzyl amine, which then transformed to the intermediary benzimidazoline. In the aerobic oxidative cyclo-dehydrogenation step, benzimidazoline was oxidized to the finally product benzimidazole. The whole process is catalyzed by $Fe_2(SO_4)_3$/TEMPO.

Conclusion

In summary, we developed a simple, and efficient method for the aerobic oxidative synthesis of 2-arylbenzimidazoles, 2-arylbenzoxazoles, and 2-arylbenzothiazoles from arylmethanols or arylmethylamines with o-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol catalyzed by $Fe_2(SO_4)_3$/TEMPO system under solvent-free conditions at 100 °C. This practical reaction uses air as an economic and green oxidant, tolerates a variety of functional groups on the aromatic ring of the benzylic partner, and affords the products in moderate yields.

Experimental section

All starting materials were purchased from commercial sources and used without further treatment. Melting



Scheme 1 A possible mechanism for $Fe_2(SO_4)_3$/TEMPO aerobic catalytic oxidative synthesis of benzimidazoles from benzyl amine or benzyl alcohol with *o*-phenylenediamine

points were determined on a Thomas Hoover capillary apparatus and are uncorrected. All known compounds were identified by appropriate technique such as ^{1}H NMR and compared with previously reported data. ^{1}H NMR (500 MHz) was recorded on a Bruker 500 spectrometer with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on an Agilent technologies 6110 quadrupole LC/MS equipped with an electrospray ionization (ESI) probe operating in positive ion mode. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. Yields refer to the isolated yields of the products after purification by silica gel column chromatography (300 mesh).

Typical procedure for aerobic oxidative synthesis of benzimidazoles, benzoxazoles, or benzothiazoles

A mixture of 6 mmol of the alcohol or the amine and 5 mmol *o*-phenylenediamine, *o*-aminophenol or *o*-aminothiophenol, 10 mol % $Fe_2(SO_4)_3$, 10 mol % TEMPO was prepared in a 10 ml three-necked flask, and then stirred in open air at 110 °C for several hours, The reaction progress was monitored by TLC. When the final reaction mixture cooled to room temperature, the crude products was directly purified by column chromatography on silica gel using hexane/ethyl acetate (7:3) as eluent to afford the pure product.

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