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One-pot Synthesis of Benzimidazoles and Benzothiazoles in the Presence of $Fe(HSO_4)_3$ as a New and Efficient Oxidant

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A series of substituted benzimidazoles and benzothiazoles were prepared through the one-pot reaction of *o*-phenylenediamine and *o*-aminothiophenol with various aldehydes in the presence of ferric hydrogensulfate both in EtOH and water as solvent. The reactions proceed smoothly in excellent yield, high chemoselectivity and with an easy work-up.

Key Words : Benzimidazole, Benzothiazole, $Fe(HSO_4)_3$, Aldehyde

Introduction

There is a continuing interest in preparing of benzimidazole and benzothiazole-containing structures. Benzimidazoles have been used as antitumor,[1] antimicrobial agents,[2] antivirus,[3] topoisomerase I inhibitors,[4] selective neuropeptide Y Y1 receptor antagonists,[5,6] and angiotensin II inhibitors[7] while benzothiazoles are important as antitumor,[8] antimicrobial agents[9] and LTD_4 receptor antagonist.[10] Despite their importance of these heterocyclic moieties from pharmacological, industrial, and synthetic points of view, comparatively few methods for the preparation of benzimidazoles and benzothiazoles have been reported.

The literature assay shows that the two general methods for the synthesis of benzimidazoles and benzothiazoles are the acidic cyclocondensation of *o*-phenylenediamine or *o*-aminothiophenol with carboxylic acids or their derivatives and oxidative cyclo-dehydrogenation of *o*-phenylenediamin or *o*-aminothiophenol with aldehydes.[11] Various oxidative reagents such as DDQ,[12] $NaHSO_{3(aq)}$,[13] nitrobenzene,[14] MnO_2,[15] 1,4-benzoquinone,[16] benzofuroxan,[17] tetracyanoethylene,[18] $Pb(OAc)_4$[19] and Oxone[20] have been employed for the synthesis of benzimidazoles and benzothiazoles. However, a number of these methods have some drawbacks such as low yields, long reaction times, drastic reaction conditions, tedious work-up procedures, and co-occurrence of several side reactions.

Promoted by the need for finding another new and efficient method for the synthesis of these heterocyclic compounds and in continuations of our previous work,[21-25] we became interested in the synthesis of 2-substituted benzimidazoles and benzothiazoles by the condensation of *o*-phenylenediamine and *o*-aminothiophenol with various aldehydes in the presence of ferric hydrogensulphate (FHS) as an oxidative catalyst.

Experimental

General Procedure for the Preparation of Benzimidazoles 1(a-m). A mixture of *o*-phenylenediamine (1 mmol), aryl aldehyde (1 mmol) and FHS (1 mmol) in appropriate solvent (EtOH or H_2O) (10 mL) were stirred at room temperature. The progress of the reaction was followed by TLC. After the completion of the reaction, water (20 mL) was added. The resulting precipitate was filtered, washed with hot water. These products were pure enough but further purification can be obtained by recrystallization from ethanol.

5-Chloro-2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole (Table 1, Entry 20): ^{1}H NMR (DMSO-d_6, 100 MHz): δ 3.75 (s, 3H), 6.92 (d, J = 9.2 Hz, 2H), 7.35 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.86 (s, 1H), 7.97 (d, J = 9.2 Hz, 2H); IR (KBr, cm^{-1}): ν 3356, 3178, 1635, 869; *m/z* 275 (M^+), 277 (M^+ + 2); Anal. Calcd. for $C_{14}H_{14}ClN_3O$ (%): C, 60.98; H, 5.12; N, 15.24. Found: C, 60.88; H, 5.02; N, 15.20.

5-Chloro-2-(4-nitrophenyl)-1*H*-benzo[*d*]imidazole (Table 1, Entry 21): ^{1}H NMR (DMSO-d_6, 100 MHz): δ 7.32 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.85 (s, 1H), 7.96 (d, J = 9.4 Hz, 2H), 8.52 (d, J = 9.4 Hz, 2H); IR (KBr, cm^{-1}): ν 3374, 3108, 1604, 1515, 1348, 857; *m/z* 273 (M^+), 275 (M^+ + 2); Anal. Calcd. for $C_{13}H_8ClN_3O_2$ (%): C, 57.05; H, 2.95; N, 15.35. Found: C, 56.94; H, 2.90; N, 15.29.

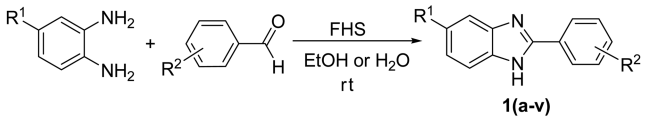
5-Chloro-2-(4-*N*,*N*-dimethylaminophenyl)-1*H*-benzo[*d*]-imidazole (Table 1, Entry 22): ^{1}H NMR (DMSO-d_6, 100 MHz): δ 3.35 (s, 6H), 6.82 (d, J = 8.9 Hz, 2H), 7.37 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.85 (s, 1H), 7.94 (d, J = 8.9 Hz, 2H); IR (KBr, cm^{-1}): ν 3456, 3047, 2917, 1607, 820; *m/z* 271 (M^+), 273 (M^+ + 2); Anal. Calcd. for $C_{15}H_{14}ClN_3$ (%): C, 66.30; H, 5.19; N, 15.46. Found: C, 66.22; H, 5.05; N, 15.42.

General Procedure for the Preparation of Benzothiazoles 2(a-m). A mixture of *o*-aminobenzenethiol (1 mmol), an appropriate aldehyde (1 mmol) and FHS (1 mmol) in EtOH (10 mL) were heated under reflux conditions. The progress of the reaction was monitored by TLC. When the reaction was completed, the mixture was cooled to room temperature and water (20 mL) was added to the mixture. The resulting solid product was filtered and washed with hot water.

Results and Discussion

FHS is a cheap and easily prepared acidic and oxidizing agent has been synthesized according to our previously published method,[26] but its application as an oxidant in the synthesis of 2-arylbenzimidazoles and 2-arylbenzothiazoles has not been studied. In order to study the effect of solvent on the rate and yield of reaction, we performed a set of preliminary experiments on the reaction of *o*-phenylenediamine and *o*-aminothiophenol with *p*-methoxybenzaldehyde in the presence of FHS as a model experiment in different solvents such as EtOH, MeOH, CH_3CN, HOAc and $CHCl_3$. The observed results showed that ethanol is the best organic solvent for the reaction.

This study shows that FHS is an efficient oxidant in the synthesis of 2-arylbenzimidazoles and 2-arylbenzothiazoles. 2-Arylbenzimidazoles are obtained by the condensation reaction of 1,2-phenylenediamine with different aromatic aldehydes in ethanol at room temperature (Scheme 1). A variety of aromatic aldehydes bearing electron-donating (entries 2-7, 14, 16, 18, 20, 22) and electron-withdrawing substituents (entries 11-13, 17, 21) are successfully used to prepare the corresponding benzimidazole derivatives in excellent yields (Table 1). Electron-withdrawing groups on benzaldehyde accelerate the reaction rate in comparison to electron-donating groups which decrease the rate. Substitution on *ortho* position of aldehydes decreases the rate which their reactions were completed in longer times. On the other hand, electron-withdrawing group on *o*-phenylenediamine ring extended the reaction times to 50-80 min.



Scheme 1

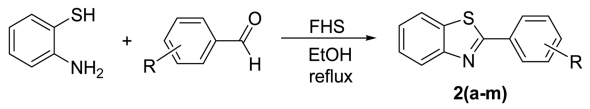
In order to explore an environmentally friendly green chemistry, we promoted the study on the use of water as solvent for the synthesis of 2-substituted benzimidazoles. Thus, we examined the treatment of differently substituted aldehydes depicted in Table 1 and *o*-phenylenediamines for the synthesis of benzimidazoles. Equal molar amount of phenylenediamines and aryl aldehydes were treated at room temperature in the presence of FHS for the periods of time indicated in Table 1. Although all the aldehydes and *o*-phenylenediamines examined are reacted to form the desired products, the yields were relatively lower and the reaction times were a bit longer.

Encouraged by these results and in order to extend the generality of this method, the reaction of *o*-aminothiophenol with benzaldehyde in the presence of FHS in ethanol and water individually as optimized solvents was studied. Preliminary studies showed that the titled reaction was failed at room temperature and needed higher ones. However, the corresponding benzothiazoles were obtained in boiling ethanol and water in 91% and 25% yield, respectively. Low yield of model reaction in water may be due to low solubility of *o*-aminothiophenol rather than *o*-phenylenediamine in water.

Table 1. Synthesis of benzimidazoles **1(a-v)**

Entry	R1	R2	Time (min)		Yield (%)[a]		mp (ºC)	mp (ºC) [lit.]
			Water	EtOH	Water	EtOH		
1	H	H	30	25	93	95	288-289	287-288[27a]
2	H	4-CH_3-	45	30	90	90	293-294	295-296[27a]
3	H	4-$(CH_3)_2CH$-	75	50	75	80	249-250	250-251[27b]
4	H	2-CH_3O-	60	50	80	82	133-135	155-158[27c]
5	H	4-CH_3O-	45	35	90	91	231	230-232[27a]
6	H	4-$(CH_3)_2N$-	45	40	90	95	292-294	294-296[27d]
7	H	4-$(CH_3CH_2)_2N$-	55	40	90	90	223-232	232[27e]
8	H	3-OH-	50	50	93	91	183-184	182-183[27b]
9	H	2-OH-	60	70	90	88	241-243	242-243[27a]
10	H	2-Cl-	75	60	85	90	227-229	227[27a]
11	H	4-Cl-	60	30	91	94	281-283	282-285[27a]
12	H	3-NO_2-	45	25	95	97	185-187	184-187[27a]
13	H	4-NO_2-	60	20	93	98	310	308-310[27a]
14	H	2-OH-3-CH_3O-	50	45	90	93	270-272	270-271[27f]
15	4-NO_2-	H	80	75	80	85	203-204	203-205[27g]
16	4-NO_2-	4-CH_3O-	100	80	85	89	236-239	237-238[27h]
17	4-NO_2-	4-NO_2-	90	75	90	93	335-336	338-339[27h]
18	4-NO_2-	4-$(CH_3)_2N$-	100	80	87	91	225-227	228-230[27i]
19	4-Cl-	H	70	50	90	90	218-220	216-218[27j]
20	4-Cl-	4-CH_3O-	75	60	91	88	278-279	-
21	4-Cl-	4-NO_2-	80	50	90	91	260-261	-
22	4-Cl-	4-$(CH_3)_2N$-	75	60	81	84	310-312	-

[a]Isolated yields. All the compounds gave satisfactory ^1H NMR and IR spectra.



Scheme 2

Table 2. Synthesis of benzothiazoles **2(a-m)**

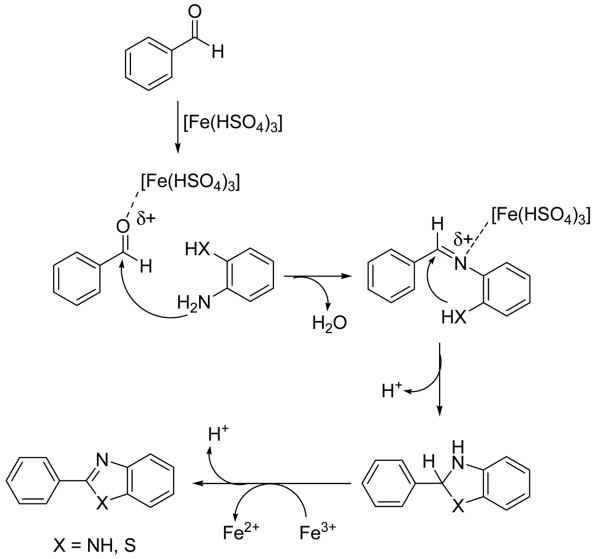
Entry	R	Time (min)	Yield (%)[a]	mp (ºC)	mp (ºC) [lit.]
1	H	20	91	111-113	110-112[28a]
2	4-CH_3-	30	88	83-85	85-87[28a]
3	4-$(CH_3)_2$CH-	45	82	73-75	74-75[28b]
4	2-CH_3O-	40	90	100-101	99-102[28a]
5	4-CH_3O-	50	94	120-122	119-121[28a]
6	4-$(CH_3)_2N$-	20	96	171-172	173-174[28c]
7	4-$(CH_3CH_2)_2N$-	25	94	122-124	124-126[28b]
8	2-OH-	30	90	131	131-132[28d]
9	2-Cl-	50	89	71-73	72-74[28e]
10	4-Cl-	30	94	114-116	116-117[28a]
11	3-NO_2-	25	96	183-185	182-184[28a]
12	4-NO_2-	20	95	194-196	195-196[28a]
13	2-OH-3-CH_3O-	30	91	162-163	162[28f]

[a]Isolated yields. All the compounds gave satisfactory ^{1}H NMR and IR spectra.

Perhaps, water reverses the reaction of carbonyl group with soft thiol nucleophile. We think that NH_2 group nucleophile is masked by hydrogen bonding in water and relatively free thiol group attacks to carbonyl group which easily reversed by water attack.

Thus, a variety of aromatic aldehydes including electron-withdrawing and electron-donating groups were investigated using the new protocol (Scheme 2). The results in Table 2 showed the reactions can be completed in ethanol in relatively short period of times with good to excellent yields.

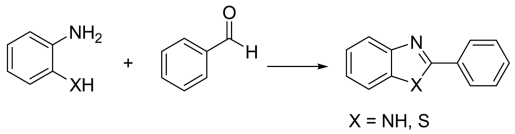
At this protocol which was carried out in reflux condition, we do not observe any significant substitution effect according to reaction times. It is noteworthy to mention that in the absence of catalyst, no product was found even after 12 h in both above established protocols for preparation of benzimidazoles and benzothiazoles. These results indicate that the catalyst plays an important role in this transformation. Accordingly, we proposed the following mechanism for explanation of above finding (Scheme 3). The bifunctional FHS catalyst, having Lewis acidic ferric cation and Bronsted acidic hydrogensulfate function, mediates the carbonyl condensation. Finally, by an oxidative dehydrogenation complete the reaction in order to obtain the aromatic benzimidazole and benzothiazole compounds.



Scheme 3

In order to demonstrate the merit of the present work in comparison with other reported results in the literature, we compared the results and reaction conditions of FHS with some other methods reported in the literature used in the synthesis of 2-phenyl-benzimidazole and 2-phenyl-benzothiazole (Table 3). As shown in Table 3, FHS is an effective catalyst with respect to reaction times, yields, and condi-

Table 3. The comparison of some other methods with FHS catalyst



Entry	XH	Time (min)	Temp. (ºC)	Yield (%)	Conditions	Literature
1	NH	35	rt	97	30% H_2O_2 (7 mmol), 37% HCl (3.5 mmol)	[29]
2	NH	16h	100	85	Solvent is dioxane and the reaction is performed in a sealed tube flushed with air	[30]
3	NH	30	rt	90	$BF_3.OEt_2$ (10% mol). The crude products were purified by silica gel column chromatography	[31]
4	NH	5h	rt	85	$Me_2S.Br_2$, CH_3CN	[32]
5	NH	15	150	79	PS-PPh_3, CCl_3CN, CH_3CN, MW	[33]
6	NH	30	rt	93	-[a]	-
7	S	15	rt	88	aq. 30% H_2O_2 (7 mmol) and SiO_2-$FeCl_3$ (0.02 g per 1 mmol of substrate)	[34]
8	S	5	140	86	MnO_2, SiO_2, MW	[35]
9	S	20	78	91	-[a]	-

[a]Reaction conditions as exemplified in experimental section

tions.

In summary, FHS has been employed as a novel, mild and efficient catalyst and oxidant for the convenient preparation of benzimidazoles and benzothiazoles in good to excellent yields from the treatment of *o*-phenylenediamine and *o*-aminothiophenol with various aldehydes, respectively. This method has several advantages like short reaction time, easy and quick work-up and excellent chemoselectivity. Also, by using FHS as catalyst, the mentioned reactions do not need toxic solvents and do not give environmentally harmful by-products.

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