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A SIMPLE AND EFFICIENT METHOD FOR SYNTHESIS OF BENZIMIDAZOLES USING $FeBr_3$ or $Fe(NO_3)_3 \cdot 9H_2O$ AS CATALYST

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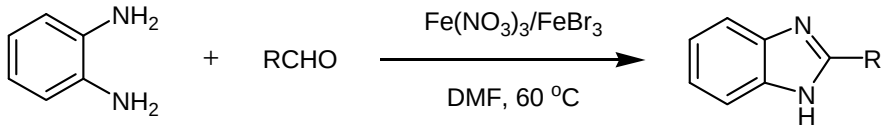
Abstract –2-Substituted benzimidazoles have been synthesized in good yields in a single pot from *o*-phenylenediamine and aldehydes using $FeBr_3$ or $Fe(NO_3)_3 \cdot 9H_2O$ as catalyst. The salient features of this method include a simple procedure, mild conditions, shorter reaction time, less toxic catalyst and easy purification.

Benzimidazoles are very useful intermediates for the development of molecules of pharmaceutical or biological interest. Benzimidazole derivatives exhibit significant activity against several viruses such as HIV,[1] herpes (HSV-1),[2] RNA,[3] influenza,[4a] and human cytomegalovirus (HCMV).[1] The widespread interest in benzimidazole-containing structures has promoted extensive studies for their synthesis. While many strategies are available for benzimidazole synthesis,[7-16] there are two general routes for the synthesis of 2-substituted benzimidazoles. One is the coupling of phenylenediamines and carboxylic acids[4b] or their derivatives (nitriles, imidates, or orthoesters),[5] which often requires strong acidic conditions, and sometimes combines with very high temperatures or the use of microwave irradiation.[6] The other way involves a two-step procedure that includes the oxidative cyclo-dehydrogenation of Schiff 's bases, which are often generated from the condensation of phenylenediamines and aldehydes. Various oxidative and catalytic reagents such as sulfamic acid,[7] I_2,[8] DDQ,[9] Air,[10] Oxone,[11] $In(OTf)_3$,[12] $Yb(OTf)_3$,[13] $Sc(OTf)_3$,[14] $KHSO_4$,[15] IL,[16] Me_2SBrBr,[17] IBD,[18] H_2O_2/HCl,[19] have been employed. Because of the availability of a vast number of aldehydes, the latter method has been extensively used. While many published methods are effective, some of these methods suffer from one or more disadvantages such as high reaction temperature, prolonged reaction time, and toxic solvents etc. Therefore, the

discovery of mild and practical routes for synthesis of 2-substituted benzimidazoles continues to attract the attention of researchers.

The reactivity of Fe^{3+} in organic synthesis has been extensively studied.[20] The aim of our work was to develop a simple and general procedure for synthesis of benzimidazoles. So we tried to synthesize benzimidazoles using $FeBr_3$ and $Fe(NO_3)_3 \cdot 9H_2O$ as catalyst (Equation 1).



Equation 1

In order to establish the optimum conditions for this reaction, various ratio of $FeBr_3$ and $Fe(NO_3)_3 \cdot 9H_2O$ were examined. Using *o*-phenylenediamine and *p*-chlorobenzaldehyde as a model, $FeBr_3$ or $Fe(NO_3)_3 \cdot 9H_2O$ was added in various ratio in DMF at 60 °C. As shown in Table 1, a few desired products were obtained in the absence of $FeBr_3$ and $Fe(NO_3)_3 \cdot 9H_2O$. Substrates and intermediates could not be converted efficiently with too less $FeBr_3$ or $Fe(NO_3)_3 \cdot 9H_2O$ and more by-products were obtained with too much $FeBr_3$ or $Fe(NO_3)_3 \cdot 9H_2O$, higher yield was given in the presence of 5 mol % $FeBr_3$ or 10 mol % $Fe(NO_3)_3 \cdot 9H_2O$. When $FeBr_3$ (5 mol %) and $Fe(NO_3)_3 \cdot 9H_2O$ (10 mol %) were used, no improved yield was obtained. Little benzimidazole was obtained if this reaction was operated in nitrogen atmosphere (Table 1, Entry 11-13). That 's to say, O_2 played an important role in this reaction.

Table1**.** Various ratio of $FeBr_3$ or $Fe(NO_3)_3 \cdot 9H_2O$ in synthesis 2-(4-chlorophenyl)benzimidazole

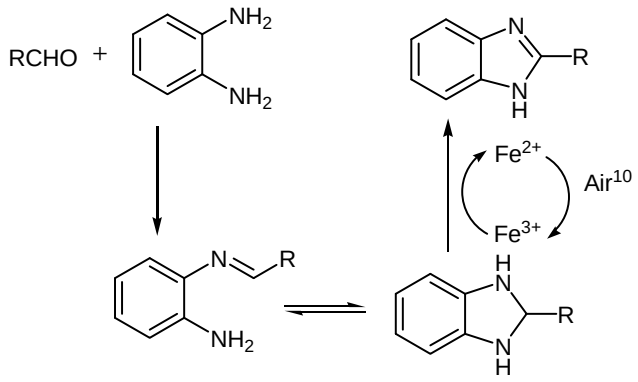
Entry	$FeBr_3$ (mol %)	$Fe(NO_3)_3 \cdot 9H_2O$ (mol %)	Time (min)[b]	Yield (%)[a]
1	0	0	25	<10
2	0	3	25	65
3	0	6	25	73
4	0	10	25	80
5	0	15	25	75
6	3	0	25	60
7	5	0	25	81
8	10	0	25	70
9	15	0	25	50
10	5	10	25	81
11[c]	0	10	25	29
12[c]	5	0	25	30
13[c]	5	10	25	30

[a]All yields refer to isolated product (no improved yield with longer reaction time).

[b]After the reaction mixture was added with $FeBr_3$ or $Fe(NO_3)_3 \cdot 9H_2O$.

[c]Operated in nitrogen atmosphere.

The possible mechanism are shown below.



Using the present method, we also investigated the result of other substituted benzaldehyde. It is noteworthy that in the present reaction conditions only the desired benzimidazoles were isolated, except in the case of 8, 9. When the two aldehydes as substrates, benzimidazoles were obtained in lower yield. Even so, the yields were still acceptable. Aliphatic aldehyde was less reactive than arylaldehyde in this reaction, so little aimed product was obtained when aliphatic aldehyde was used. The results were summarized in Table 2 and Table 3.

Table 2**.** Synthesis of benzimidazoles in DMF using $FeBr_3$ (5 mol %) as catalyst

Entry	R	Time[b] (min)	Yield[a] (%)
1	C_6H_5	25	88
2	4-ClC_6H_4	25	81
3	4-$NO_2C_6H_4$	45	78
4	3-$NO_2C_6H_4$	40	82
5	2-OHC_6H_4	45	75
6	4-$CH_3C_6H_4$	25	83
7	4-$CH_3OC_6H_4$	55	73
8	2-furyl	35	54
9	C_6H_5CH=CH	35	51
10	CH_3 $(CH_2)_5$	60	trace
11	$CH_3CH_2CH_2$	60	trace
12	CH_3CH_2	60	trace

[a]All yields refer to isolated product, characterized by melting points, ^{1}H NMR.

[b]After the reaction mixture was added with $FeBr_3$.

Table 3**.** Synthesis of benzimidazoles in DMF using $Fe(NO_3)_3 \cdot 9H_2O$ (10 mol %) as catalyst

Entry	R	Time[b] (min)	Yield[a] (%)
1	C_6H_5	25	85
2	4-ClC_6H_4	25	80
3	4-$NO_2C_6H_4$	40	77
4	3-$NO_2C_6H_4$	100	77
5	2-OHC_6H_4	35	76
6	4-$CH_3C_6H_4$	25	80
7	4-$CH_3OC_6H_4$	40	70
8	2-furyl	40	50
9	$C_6H_5CH{=}CH$	25	48
10	CH_3 $(CH_2)_5$	60	trace
11	$CH_3CH_2CH_2$	60	trace
12	CH_3CH_2	60	trace

[a]All yields refer to isolated product, characterized by melting points, ^{1}H NMR. [b]After the reaction mixture was added with $Fe(NO_3)_3 \cdot 9H_2O$.

In conclusion, we have developed a simple, one-pot synthesis of 2-substituted benzimidazole by the condensation of *o*-phenylenediamine with aldehyde promoted by $Fe(NO_3)_3 \cdot 9H_2O$ or $FeBr_3$. Mild and manipulable procedure, available and less toxic catalyst, easy purification and shorter reaction time are the advantageous features of this method.

EXPERIMENTAL

All melting points were determined on a Kofler micro melting point apparatus and were uncorrected. IR spectra were recorded on a SP3-300 spectrophotometer using KBr discs. ^{1}H NMR spectra were measured on a Bruker DPX-400M spectrophotometer using TMS as internal standard and $CDCl_3$ as solvent.

Typical procedure for synthesis of benzimidazoles: Typical procedure for synthesis of benzimidazoles: A solution of 4-chlorobenzaldehyde (1 mmol) and *o*-phenylenediamine (1 mmol) in DMF (2 mL) was heated at 60 °C and stirred for about 30min. Then 0.1 mmol $Fe(NO_3)_3 \cdot 9H_2O$ or 0.05 mmol $FeBr_3$ in DMF (1 mL) was added dropwise to the above solution. When the reaction was finished (monitored by TLC), the solution was cooled to room temperature and added with water (30 ml). The precipitate was filtrated and washed with water. After vacuum drying, the crude products was purified by column chromatography over silica gel (cyclohexane:ethyl acetate, 3:1) to afford the corresponding benzimidazole.

All the compounds are known compounds. They were identified from their ^{1}H NMR spectroscopic data and by comparing their mps with those reported in the literature (references cited). **1**: mp 287-288 °C (lit.,[21a] 292 °C); **2**: mp 288-291 °C (lit.,[21a] 294 °C); **3:** mp 308-310 °C (lit.,[21a] 316 °C); **4**: mp 200-202 °C

(lit.,[21b] 204-206 °C); **5**: mp 234-236 °C (lit.,[21a] 234 °C); **6**: mp 261-263 °C (lit.,[21a] 270 °C); **7**: mp 228-230 °C (lit.,[21a] 226 °C); **8**: mp 284-286 °C (lit.,[21a] 288 °C); **9**: mp 199-201 °C (lit.,[21a] 203-205 °C);

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