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A SIMPLE $KHSO_4$ PROMOTED SYNTHESIS OF 2-ARYLSUBSTITUTED BENZIMIDAZOLES BY OXIDATIVE CONDENSATION OF ALDEHYDES WITH *o*-PHENYLENEDIAMINE

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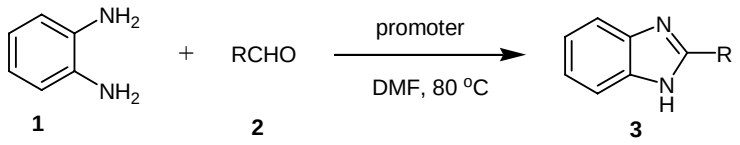
Abstract — $KHSO_4$ is used to promote the oxidative condensation of *o*-phenylenediamine with aldehydes in DMF and afford corresponding 2-substituted benzimidazoles efficiently. Simple and convenient procedure, use of inexpensive promoter, easy purification and shorter reaction time are the advantageous features of this method.

2-Substituted 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.[7-14] There are two general methods 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] $FeCl_3 \cdot 6H_2O$,[12] ionic liquid,[13] $In(OTf)_3$,[14] $Yb(OTf)_3$,[15] $Sc(OTf)_3$,[16] have been employed. Because of the availability of a vast number of aldehydes, the later 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 aim of our work was to develop a simple and convenient procedure for synthesis of benzimidazoles. Urea-hydrogen peroxide is a stable, eco-friendly and easily handled reagent in organic synthesis.[17] We tried to synthesize benzimidazoles using urea-hydrogen peroxide as oxidant, but failed. However, we found that $KHSO_4$ was a efficient promoter in synthesis of 2-substituted benzimidazoles (**3**) by the condensation of arylaldehyde (**2**: R=Ar) and cinnamicaldehyde (**2**: R=C_6H_5CH=CH-) with *o*-phenyl-enediamine (**1**) (Scheme 1).



1 **2** **3**

Scheme 1

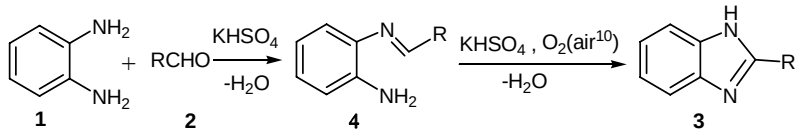
In order to establish the optimum condition for this reaction, various promoters and various solvents were examined. Using *o*-phenylenediamine (**1**) and 4-chlorobenzaldehyde (**2b**) as a model, various promoter was added in DMF at 80 °C. As shown in Table 1, different results were obtained with different promoter. 30 mol % $KHSO_4$ or $NaHSO_4$ was the best promoter in this reaction. The use of less than 30 mol % $KHSO_4$ took longer to react and more by-product were obtained with too much $KHSO_4$. Next the effect of solvent was examined. As shown in Table 2, different solvents might cause different yields. With the increase in the boiling point of solvents, the product we got also increases, except for the case of xylene. Alcoholic solvents (methanol and ethanol) and DMSO gave good yields. Clearly DMF stands out as the solvent of choice, with its fast conversion, high yield and less toxic.

Table1. Variation of promoter in condensation of *o*-phenylenediamine (**1**) with 4-chlorobenzaldehyde (**2b**)

Entry	Promoter	mmol% (Promoter)	pK_a(Promoter)	Time (min)	**3b**: Yield[a] (%)
1	A[b]	100	-	20	trace
2	A	200	-	20	trace
3	A	500	-	20	trace
4	A+$KHSO_4$	100+30	-	14-15	82
5	$KHSO_4$	30	1.92	14-15	82
6	$NaHSO_4$	30	1.92	14-15	81
7	NaH_2PO_4	30	7.21	15	trace
8	NaH_2PO_4	100	7.21	15	trace
9	KH_2PO_4	100	7.21	15	trace
10	Na_2HPO_4	100	12.66	15	trace
11	$NaHCO_3$	100	10.32	15	trace
12	$KHSO_4(N_2)$[c]	30	1.92	15	30
13	-	-	-	15	trace

[a]All yields refer to isolated **3b**. [b] A= $CO(NH_2)_2{\cdot}H_2O_2$.[c] Operated in nitrogen atmosphere.

The possible mechanism are shown below (Scheme 2).



$HSO_4^- \rightleftharpoons SO_4^{2-} + H^+$ $pK_a = 1.92$

Scheme 2

Table 2**.** Effect of solvent in condensation of *o*-phenylenediamine (**1**) with 4-chlorobenzaldehyde (**2b**)

Entry	Solvent	Conditions[b]	**3b**: Yield [a] (%)
1	CH_2Cl_2	reflux	18
2	THF	reflux	33
3	CH_3OH	reflux	57
4	CH_3CH_2OH	reflux	64
5	H_2O	80°C	54
6	DMSO	80°C	78
7	Xylene	80°C	30
8	DMF	80°C	82

[a] All yields refer to isolated product. [b] Reaction time: 15 min

To test the general scope and versatility of this procedure in the synthesis of a variety of 2-substituted benzimidazole, we examined a number of differently substituted arylaldehydes. We are pleased to find that moderate to high yields were obtained in the condensation of *o*-phenylenediamine with aldehydes. As Table 3 shows, arylaldehydes bearing both electron-donating and electron-withdrawing substituents gave desired benzimidazoles in excellent yields. Heteroarylaldehyde (**2h**) (Entry 8) and α,β-unsaturated cinnamicaldehyde (**2i**) (Entry 9) gave acceptable yields. Little product was obtained when aliphatic aldehyde was used. To extend the scope of this method, we examined the condensation of arylcarboxylic acid and *o*-phenylenediamine (**1**), but failed. We also tried to synthesize 2-arylsubstituted benzothiazoles and benzoxazoles using this method, but little product were obtained.

Table 3**.** Synthesis of benzimidazoles catalyzed and oxidized by $KHSO_4$

Entry	**2**	Time (min)	**3**: Yield [a] (%)
1	(**a**) : C_6H_5	15	(**a**) :87
2	(**b**) : 4-ClC_6H_4	15	(**b**) :82
3	(**c**) :4-$NO_2C_6H_4$	45	(**c**) :73
4	(**d**) :3-$NO_2C_6H_4$	30	(**d**) :81
5	(**e**) :2-HOC_6H_4	40	(**e**) :78
6	(**f**) :4-$CH_3C_6H_4$	15	(**f**) :80
7	(**g**) :4-$CH_3OC_6H_4$	30	(**g**) :79
8	(**h**) :2-furyl	10	(**h**) :58
9	(**i**) :C_6H_5CH=CH	10	(**i**) :50
10	(**j**) :CH_3 $(CH_2)_5$	120	(**j**) :trace
11	(**k**) :$CH_3CH_2CH_2$	120	(**k**) :trace
12	(**l**) :C_6H_5COOH[b]	120	(**l**) :0
13	(**m**) :4-ClC_6H_4COOH[b]	120	(**m**) :0

[a]All yields refer to isolated product, characterized by melting points, GC-MS, IR, ^{1}H NMR.
[b]We tried to use arylcarboxylic acid as the substrtate, but failed.

In conclusion, we have developed a simple, one-pot synthesis of 2-arylsubstituted benzimidazoles (**3**) by the condensation of *o*-phenylenediamine (**1**) with arylaldehyde (**2**) promoted by $KHSO_4$. Simple and convenient procedure, use of inexpensive promoter, 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 DMSO as solvent.

Typical procedure for synthesis of benzimidazoles: *o*-Phenylenediamine (**1**) (0.5 mmol) and aldehyde (**2**) (0.5 mmol)were mixed in DMF (1.5 mL) thoroughly, then $KHSO_4$ (0.17 mmol) was added, heated and stirred at 80 °C for appropriate time (monitored by TLC). When the reaction was finished, the solution was cooled to rt. The reaction mixture was added dropwise with vigorous stirring into a mixture of Na_2CO_3 (0.17 mmol) and H_2O (20 mL). In cases where the product (**3**) precipitated as a free flowing solid (Table 3, Entries 1-6), it was collected by filtration, washed with H_2O and dried. In cases where gummy material precipitated the product (**3**) (Table 3, Entries 7-9) was extracted into EtOAc, the organic phace was washed with H_2O, brine and dried (Na_2SO4). Evaporation of solvent gave the crude product, the crude products were purified by column chromatography over SiO_2 (cyclohexane:AcOEt 3:1) to afford the corresponding benzimidazole (**3**).

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). **3a**: mp 287-288 °C (lit.,[18a] 292 °C); **3b**: mp 288-291 °C (lit.,[18a] 294 °C); **3c**: mp 308-310 °C (lit.,[18a] 316 °C); **3d**: mp 200-202 °C (lit.,[18b] 204-206 °C); **3e**: mp 240-242 °C (lit.,[18a] 242 °C); **3f**: mp 261-263 °C (lit.,[18a] 270 °C); **3g**: mp 228-230 °C (lit.,[18a] 226 °C); **3h**: mp 284-286 °C (lit.,[18a] 288 °C); **3i**: mp 199-201 °C (lit.,[18a] 203-205 °C).

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