Full paper

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Synthesis of 2-aryl-1-arylmethyl-1H-1, 3-benzimidazoles catalysed by ferric ammonium sulfate ($NH_4Fe(SO_4)_2$) under solvent-free conditions

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$NH_4Fe(SO_4)_2$ was found to be a mild and effective catalyst for the selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles under solvent-free conditions. Copyright © 2015 John Wiley & Sons, Ltd.

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Keywords: 2-aryl-1-arylmethyl-1H-1,3-benzimidazoles; o-phenylenediamine; ferric ammonium sulfate; solvent-free

Introduction

Benzimidazole derivatives are widely used in medicinal chemistry because of their diverse biological activity and clinical applications.[1] These bicyclic compounds consist of the fusion of benzene and imidazole. The most prominent benzimidazole compound in nature is *N*-ribosyldimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B_{12}.[2] Benzimidazoles, as an extension of the well-elaborated imidazole system, have been used as carbon skeletons for *N*-heterocyclic carbenes.[3] The *N*-heterocyclic carbenes are usually used as ligands for transition metal complexes. They are often prepared by deprotonating an *N,N'*-disubstituted benzimidazolium salt at the 2-position with a base.[4] Substituted benzimidazole derivatives have found applications as diverse therapeutic agents, including anti-ulcers, anti-hypertensives, antivirals, antifungals, anti-cancers and anti-histaminics.[5–7]

Because of their importance, the synthesis of substituted benzimidazoles has become a focus of synthetic organic chemistry. Various oxidative and catalytic reagents such as 2,3-dichloro-5,6-dicyanobenzoquinone,[8] MnO_2,[9] ionic liquids,[10] alumina–methanesulfonic acid,[11] diacetoxyiodobenzene,[12] $Yb(OTf)_3$,[13] silica sulfuric acid,[14] oxalic acid,[15] *N*-bromosulfonamide,[16] *N*-iodosulfonamide,[17] Co/Mn nanoparticles,[18] 2,4,6-trichloro-1,3,5-triazine[19] and silica phenylsulfonic acid[20] have been employed to effect this transformation. However, a number of these methods have some drawbacks such as low yields, the use of expensive reagents or chlorinated organic solvents, and harsh reaction conditions.

As part of our continued interest in the development of a highly expeditious methodology[21–27] for the synthesis of fine chemicals and heterocyclic compounds of biological importance, we report a selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in water, in acetonitrile or under solvent-free conditions by the use of ferric ammonium sulfate as a catalyst (Scheme 1).

Results and discussion

In order to choose a suitable solvent, the syntheses of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles were carried out in ethanol, water, dichloromethane and acetonitrile and also under solvent-free conditions. Our findings show that solvent-free conditions are generally the best in terms of yield and reaction time (Table 1).

Table 2 summarizes the results of using various amounts of catalyst in the synthesis of 1-(2-methoxybenzyl)-2-(2-methoxyphenyl)-1*H*-benzimidazole. The best yield is obtained when 80 mg of catalyst is used.

The optimization of the reaction conditions reveals that simple stirring of the catalyst (80 mg), aldehyde (2 mmol), *o*-phenylenediamine (1 mmol) and H_2O_2 (1 mmol) effects the formation of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in quantitative yields at 70 °C (Table 3).

The results indicate that the proposed method is a selective procedure for the synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles with good to high yields. We observe that the synthesis in the presence of ferric ammonium sulfate in water or under solvent-free conditions takes place faster than that in acetonitrile. As evident from Table 3, both electron-rich and electron-deficient aldehydes react without any significant difference to give the corresponding benzimidazoles in good yield. When two equivalents of aldehyde at 70 °C are used in the reaction, 1,2-disubstituted benzimidazoles are obtained as major product, so the present method is a good procedure for selective synthesis of 2-aryl-1-arylmethyl-

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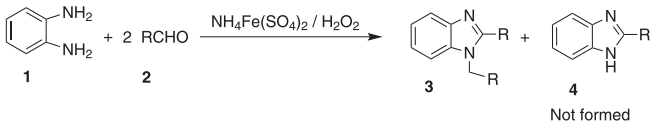


Scheme 1. Synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles.

Table 1. Effect of solvent in the synthesis of 1-(2-methoxybenzyl)-2-(2-methoxyphenyl)-1*H*-benzimidazole catalysed by ferric ammonium sulfate

Entry	Solvent[a]	Time (min)	Yield (%)[b]
1	C_2H_5OH	60	70
2	H_2O	25	92
3	CH_2Cl_2	60	45
4	CH_3CN	360	75
5	Solvent-free	10	92

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), aryl aldehyde (2 mmol), H_2O_2 (1 mmol) and $NH_4Fe(SO_4)_2$ (80 mg) in solvent under reflux.
[b]Isolated yields.

Table 2. Effect of catalyst amount[a]

Entry	Catalyst (mg)	Yield (%)
1	20	40
2	40	70
3	60	90
4	80	92
5	100	92

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), aryl aldehyde (2 mmol), H_2O_2 (1 mmol) and $NH_4Fe(SO_4)_2$.

1*H*-1,3-benzimidazole derivatives. The reusability of $NH_4Fe(SO_4)_2$ was studied for this system. The catalyst can be easily separated by dispersing the reaction mixture in dichloromethane and filtering. As evident from the data for product **3 k** in Table 3, the yield of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazole only decreases a little after the reuse of $NH_4Fe(SO_4)_2$ four times.

The proposed mechanism for the synthesis of the 1,2-disubstituted benzimidazoles may involve the iminium-catalysed formation of *N*,*N*′-dibenzylidene-*o*-phenylenediamine, activation by catalyst and ring closure, giving a five-member ring in either a sequential or a concerted manner (Scheme 2).[16]

Finally, to assess the present protocol with respect to other reported methods for the synthesis of 2-phenyl-1-phenylmethyl-1*H*-1,3-benzimidazoles, the presented procedure using $NH_4Fe(SO_4)_2$–H_2O_2 as catalyst is compared with other systems. From Table 4, it is evident that the present system gives higher conversions and yields compared to other reported systems.

Conclusions

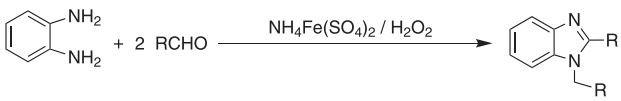
A simple protocol for the synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazole derivatives with very good yields was described. $NH_4Fe(SO_4)_2$ was found to be a mild and effective catalyst for the selective synthesis of these derivatives in water and under solvent-free conditions by the rapid condensation of various aryl aldehydes with *o*-phenylenediamine. Moreover, the method has advantages in terms of selectivity, use of inexpensive and reusable catalyst, operational simplicity (easy work-up) and environmental friendliness (non-corrosive reagent).

Experimental

General remarks

All commercially available chemicals were obtained from Merck and Fluka, and used without further purification unless otherwise

Table 3. Ferric ammonium sulfate as catalyst for synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in water, in acetonitrile and under solvent-free conditions[a]



Product[b]	R	Solvent-free		Water		Acetonitrile		M.p. (°C)
		Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	
3a	C_6H_5	7	96	10	91	7	80	130–132[28]
3b	4-MeC_6H_4	7	96	10	95	12	72	123–125[28]
3c	4-$MeOC_6H_4$	10	93	25	91	6	73	130–131[28]
3d	2-$MeOC_6H_4$	10	92	25	92	6	75	152–154[28]
3e	4-ClC_6H_4	10	95	20	93	9	70	135–137[28]
3f	2-ClC_6H_4	20	94	25	90	10	71	153–155[28]
3 g	4-$Me_2NC_6H_4$	10	95	15	92	6	70	250–252[28]
3 h	4-$NO_2C_6H_4$	15	95	25	92	6	75	184–186[29]
3i	2-$NO_2C_6H_4$	20	92	30	90	9	73	170–172[30]
3j	4-CNC_6H_4	15	90	20	91	9	70	185–186[31]
3k[c]	2-$MeOC_6H_4$	10	80					

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), aryl aldehyde (2 mmol), H_2O_2 (1 mmol) and $NH_4Fe(SO_4)_2$ (80 mg) at 70 °C.
[b]Products were characterized from their physical properties, compared with authentic samples.
[c]Catalyst reuse after three runs.

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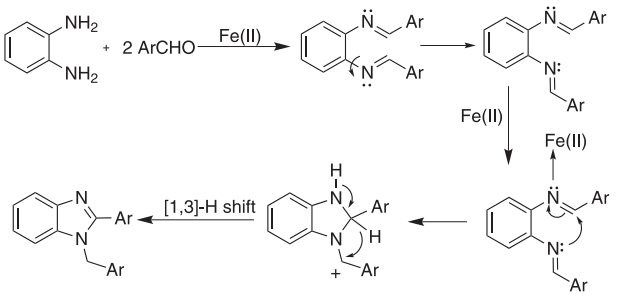

Scheme 2. Proposed mechanism for synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles.

Table 4. Comparison of efficiency of various catalysts in synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles

Entry	Catalyst	Conditions	Time (min)	Yield (%)	Ref.
1	Silica sulfuric acid	H_2O, r.t.	120	70	[14]
2	Trifluoroacetic acid	H_2O–ethanol, r.t.	25	74	[32]
3	SBA-Pr-SO_3H	Solvent-free, r.t.	25	88	[33]
4	Acetic acid	Acetic acid–O_2, 80 °C	25	92	[34]
5	K-10 clay	Solvent-free, MW	10	90	[29]
6	Amberlite IR-120	H_2O–ethanol, r.t.	100	95	[35]
7	SiO_2-Pr-SO_3H	Solvent-free, r.t.	60–120	90	[36]
8	Zn–proline	H_2O, 25 °C	120	90	[31]
9	SiO_2–$ZnCl_2$	Solvent-free, MW	20	72	[37]
10	$NH_4Fe(SO_4)_2$–H_2O_2	Solvent-free, 70 °C	7	96	This work

stated. ^{1}H NMR spectra were recorded with a Bruker 200 MHz NMR spectrometer using tetramethysilane as internal standard and chemical shifts (δ) were measured in ppm. Infrared spectra were obtained using a PerkinElmer GX FT-IR spectrometer. All yields refer to isolated products.

General procedure for synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles

A mixture of *o*-phenylenediamine (1 mmol), aryl aldehyde (2 mmol) and H_2O_2 (1 mmol) was stirred with $NH_4Fe(SO_4)_2$ (80 mg) at 70 °C for a period of time specified in Table 1. The reaction was monitored using TLC (*n*-hexane–acetone, 7:3). After completion of the reaction, H_2O (10 ml) was added, followed by extraction with CH_2Cl_2 (4 × 10 ml) and drying over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product which was recrystallized from ethanol (90%).

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