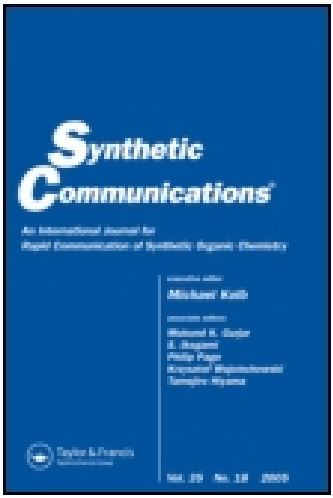

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$M(HSO_4)_n$-Promoted Synthesis of 2-Aryl-1-arylmethyl-1H-1,3-benzimidazole Derivatives

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Abstract: We have developed a highly selective synthesis of 2-aryl-1-arylmethyl-*1H*-1,3-benzimidazoles from the reaction of *o*-phenylenediamines and aromatic aldehydes in the presence of metal hydrogen sulfates [$M(HSO_4)_n$] in water and also under solvent-free conditions in good to excellent yields.

Keywords: Aryl aldehydes, benzimidazole derivatives, metal hydrogen sulfates [$M(HSO_4)_n$, 1,2-phenylenediamine, water

INTRODUCTION

In recent years, the search for environmentally benign chemical processes or methodologies has received much attention from chemists, because they are essential for the conservation of the global ecosystem. The development of heterogeneous catalysts for fine chemical synthesis has become a major area of research, as the potential advantages of these materials (simplified recovery and reusability; the potential for incorporation in continuous reactors and microreactors) over homogeneous systems can lead to novel environmentally benign chemical procedures for academia and industry.[1] From this viewpoint, the catalytic reaction is a valuable process because the use of stoichiometric reagents that are often toxic

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poses problems from both economical and environmental viewpoints regarding product purification and waste management.[2]

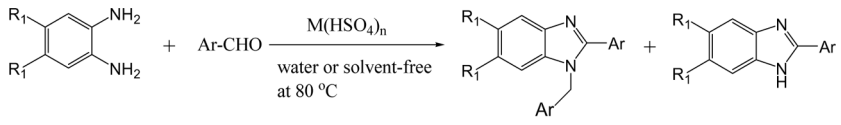
Application of solid acids in organic transformations are very important because solid acids have many advantages such as simplicity in handling, decreased reactor and plant corrosion problems, and more environmentally safe disposal. On the other hand, a reduction in the amount of liquid acid needed and/or any simplification in handling procedures is required for risk reduction, economic advantage, and environment protection.[3–13] Among solid acids, metal hydrogen sulfates $M(HSO_4)_n$[13] are alternatives for very dangerous concentrated liquid sulfuric acid, and there are several reports about using these solid acidic salts in organic transformation.

The benzimidazole nucleus is of significant importance to medicinal chemistry. Several publications report benzimidazole-containing compounds showing biological activities such as selective neuropeptide YY1 receptor antagonism[14] and as 5-lipoxygenase inhibitors for use as novel antiallergic agents,[15] factor Xa (FXa) inhibitors,[16] poly (ADP-ribose) polymerase (PARP) inhibitors,[17] and human cytomegalovirus (HCNV) inhibitors.[18] Substituted benzimidazole derivatives have found commercial applications in veterinarian medicine as anthelmintic agents and in diverse human therapeutic areas such as treatment of ulcers and as antihistamineics.[19] In light of the affinity they display toward a variety of enzymes and protein receptors, medicinal chemists would certainly classify them as ''privileged sub structures'' for drug design.[20,21]

The traditional synthesis of benzimidazoles involves the reaction between *o*-phenylenediamines and a carboxylic acid or its derivatives (nitriles, amidates, orthoesters) under harsh dehydrating conditions.[21–26] Benzimidazoles have also been prepared on solid phase to provide a combinatorial approach.[27,28] The most popular strategies for their synthesis utilize *o*-nitroanilines as intermediates or resort to direct N-alkylation of an unsubstituted benzimidazole.[29,30] A number of synthetic protocols that involve intermediate *o*-nitroanilines have evolved to include the synthesis of benzimidazoles on solid support.[31,32] Another method for the synthesis of these compounds is the reaction of *o*-phenylenediamines with aldehydes in the presence of acidic catalysts under various reaction conditions.[33–38]

In connection with our interest in the use of solid acidic salts as efficient catalysts in various transformations[6–13] and also in continuation of our studies on the preparation of benzimidazole derivatives,[39] we report here a selective synthesis of 2-aryl-1-arylmethy-1*H*-1,3-benzimidazoles in water and also under solvent-free conditions (Scheme 1).

Condensation of *o*-phenylenediamine and benzaldehyde was performed with different molar ratio of solid acids to optimize the reaction



Scheme 1. Condensation of *o*-phenylenediamine derivatives with aromatic aldehydes.

conditions. In a preliminary study, the effect of various solid acids on the yields and times of condensation was investigated with the previously mentioned substrate as a model compound. As shown in Table 1, $Al(HSO_4)_3$, $Mg(HSO_4)_2$, and $Ca(HSO_4)_2$ are the best solid acid catalysts for this purpose in water at 80 °C.

Also, $Zn(HSO_4)_2$, $NaHSO_4$, and CH_3SO_3H catalyze this condensation with a longer reaction time. The required molar ratio, 1:2:0.3, was applied for *o*-phenylenediamine, benzaldehyde, and catalyst $M(HSO_4)_n$ respectively under the previously mentioned conditions. When *o*-phenylenediamine derivatives **1** and aromatic aldehydes **2** in the presence of metal hydrogen sulfates and different organic solvents were allowed to react at 80 °C, both expected products were obtained whose ratios depended on the nature of the solvent (Scheme 1, **3** and **4**). As can be seen in Table 2, the best overall yields and selectivities were obtained in solvent-free conditions, water and ethanol, in which only N-substituted benzimidazoles **3** were produced. There is an urgent need to develop alternative solvents and technologies because of pressure from governmental organizations and other regulatory bodies to protect the

Table 1. Effect of different solid acids on the condensation of *o*-phenylenediamine (1 mmol) with benzaldehyde (2 mmol) in water at 80 °C to produce **3a**

Entry	Solid acid	Amount of catalyst (mmol)	Time (min)	Yield (%)[a]
1	$Al(HSO_4)_3$	0.1	600	50[b]
2	$Al(HSO_4)_3$	0.2	540	70[b]
3	$Al(HSO_4)_3$	0.3	150	92
4	$Mg(HSO_4)_2$	0.1	600	60[b]
5	$Mg(HSO_4)_2$	0.3	45	92
6	$Ca(HSO_4)_2$	0.3	60	90
7	$Zn(HSO_4)_2$	0.3	180	48
8	$NaHSO_4 \cdot H_2O$	0.3	170	83
9	CH_3SO_3H	0.3	210	63

[a]Isolated yields.
[b]Conversion.

Table 2. Effect of solvent on the time and yield of the reaction of *o*-phenylenediamine and benzaldehyde in the presence of $Mg(HSO_4)_2$ at 80 °C

Entry	Solvent	Time (min)	Yield (%)[a]	
			3	**4**
1	EtOH	150	90	—
2	CH_3CN	360	65	<5
3	MeOH	210	60	<10
4	CCl_4	600	—	—
5	H_2O	45	92	—
6	$C_6H_5CH_3$	600	30	<10
7	Solvent-free	10	92	—

[a]Isolated yield.

environment. Use of green solvents such as water showed both economical and synthetic advantages. Solvent-free organic reactions have been applied as a useful protocol in organic synthesis.[40] Solvent-free conditions often lead to shorter reaction times, increased yields, and easier work up, match green chemistry protocols, and may enhanced region- and stereoselectivity of the reactions.[40] Thus, we decided to investigate the reaction in water and also in solvent-free conditions. Consequently several aromatic aldehydes with different substituents on the aromatic ring were subjected to the condensation reaction. As Table 3 shows, arylaldehydes without substituents gave the desired benzimidazoles in excellent yields (**3a**, **3e**). Aldehydes bearing electron-donating substituents gave more desired benzimidazoles (**3b–3d** and **3i**) than electron-withdrawing substituents (Table 3). Arylaldehydes with electron-withdrawing substituents such as 4-nitro- or 3-nitro-benzaldehyde gave a mixture of both benzimidazoles **3**, **4** by this methodology.

As described before, compound **3** may be produced through a tandem sequence of reactions starting with the formation of dibenzylidene-o-phenylenediamine followed by ring closure.[34] Finally, aromatization took place via deprotonation and 1,3-hydride transfer (Scheme 2).[36]

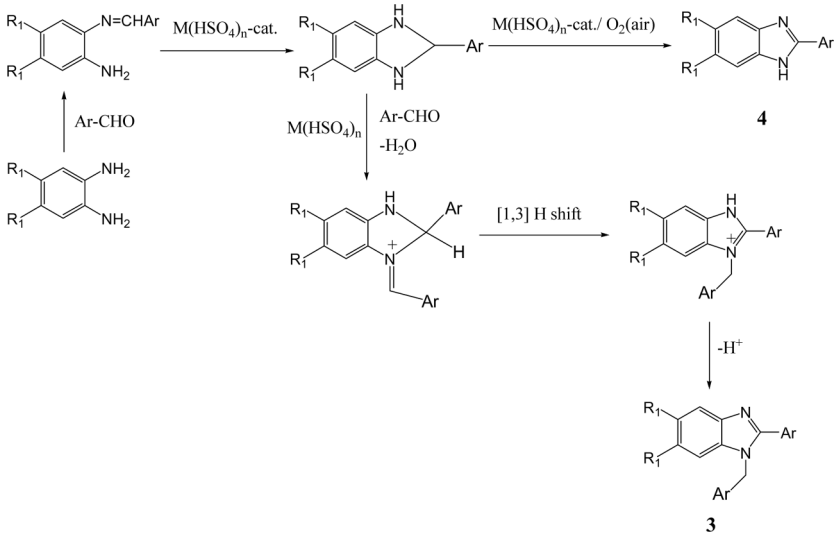
The production of monosubstituted benzimidazole **4** in some cases could be visualized to occur by condensation of *o*-phenylenediamine with the aldehyde followed by air oxidation of the dihydrobenzimidazole derivative, as previously reported.[41]

In summary, we have reported a new and effective methodology for the ecocompatible preparation of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles. The easy purification of the products by simple filtration and recrystallization, the use of water as the solvent or use of solvent-free

Table 3. Reaction of aromatic aldehydes with *o*-phenylenediamine derivatives in the presence of metal hydrogen sulfates [M = Al, (**I**); Mg, (**II**); Ca, (**III**)] under solvent-free conditions and also in water[b] at 80 °C

			Time (min)			Yield (%)[a]			
Product	R^1	R^2	**I**	**II**	**III**	**I**	**II**	**III**	Mp (°C)
3a	H	C_6H_5	15 (150)	10 (45)	25 (60)	90 (92)	92 (92)	82 (90)	132[31]
3b	H	4-Me-C_6H_4	20 (150)	15 (45)	30 (210)	88 (87)	90 (85)	90 (71)	128–130[31]
3c	H	4-MeO-C_6H_4	15 (150)	15 (150)	30 (300)	92 (90)	93 (90)	86 (82)	129–130[36]
3d	H	2-MeO-C_6H_4	20 (150)	20 (150)	35 (240)	90 (85)	89 (80)	85 (80)	152–153[36]
3e	H	2-Furyl	15 (150)	20 (150)	45 (210)	82 (81)	83 (85)	73 (82)	94[36]
3f	H	4-Cl-C_6H_4	20 (210)	20 (210)	30 (240)	87 (85)	88 (85)	80 (82)	136[32]
3g	H	2-Cl-C_6H_4	25 (210)	25 (210)	40 (240)	80 (75)	73 (75)	80 (82)	163[31]
3h	CH_3	4-Cl-C_6H_4	300 (220)	—	—	69 (93)	—	—	189–190[37]
3i	CH_3	4-Me-C_6H_4	230 (150)	—	—	68 (92)	—	—	158–160[37]

[a]Isolated yields.
[b]The times and yields are indicated in parentheses for reactions performed in water.



Scheme 2. Proposed mechanism for the condensation of phenylenediamine with arylaldehydes.

conditions, and metal hydrogen sulfates as catalysts suggest good prospects for the applicability of this process.

EXPERIMENTAL

General

Chemicals were purchased from Merck, Fluka, and Aldrich chemical companies. IR spectra were run on a Shimadzu infrared spectroscope IR-435. The ^{1}H NMR was run on Bruker Avance (DRX 500-MHz) and Bruker Avance (400-MHz) instruments. Melting points were recorded on an SMP1 melting-point apparatus in open capillary tubes and are uncorrected. With thin-layer chromatography (TLC) using silica gel SILG/UV 254 plates, the progress of the reaction was followed. The benzimidazole products were characterized by comparison of their spectral (IR, ^{1}H-NMR), TLC, and physical data with the authentic samples.[29,30,34–37]

General Procedure for the Synthesis of 2-Aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in Water

A mixture of *o*-phenylenediamine derivatives (1 mmol), aromatic aldehyde (2 mmol), and metal hydrogen sulfate (M = Al, Mg, Ca) (0.3 mmol)

was added in 5 mL of water, and the reaction was stirred in a round-bottomed flask in an oil bath at 80 °C for the appropriate time (see Table 3). The progress of the reaction was followed by TLC. After completion of the reaction, the mixture was neutralized with $NaHCO_3$ (10%). The precipitates were then filtered, washed with water (2×15 mL), and air dried to afford the desired product. Finally the crude product was recrystallized from ethanol.

General Procedure for the Synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles Under Solvent-Free Conditions

A mixture of *o*-phenylenediamine derivatives (1 mmol), aromatic aldehyde (2 mmol), and metal hydrogen sulfate (M = Al, Mg, Ca) (0.3 mmol) was mixed in a mortar, placed in a round-bottomed flask, and heated in an oil bath at 80 °C for the appropriate time (see Table 3). The progress of the reaction was followed by TLC. After completion of the reaction, the mixture was neutralized with $NaHCO_3$ (10%). The precipitates were then filtered, washed with water (3×15 mL), and air dried to afford the desired product. Finally the crude product was recrystallized from ethanol.

Selected Spectra Data

Compound (**3a**) ($C_{20}H_{16}N_2$): ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 5.61 (s, 2H), 6.29 (d, 2H, $J = 8.5$ Hz), 6.62 (d, 2H, $J = 7.2$ Hz), 7.23–7.30 (m, 10H).

Compound (**3d**) ($C_{22}H_{20}N_2O_2$): ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 3.66 (s, 3H), 3.67 (s, 3H), 5.24 (s, 2H), 6.61 (d, 1H, $J = 8.3$ Hz), 6.76 (t, 1H, $J = 7.5$ Hz), 6.91 (d, 1H, $J = 8.3$ Hz), 7.08 (t, 1H, $J = 7.5$ Hz), 7.16–7.24 (m, 4H), 7.38 (d, 1H, $J = 7.5$ Hz), 7.45 (d, 1 H, $J = 7.5$ Hz), 7.52 (t, 1H, $J = 7.5$ Hz), 7.71 (d, 1H, $J = 7.5$ Hz).^{13}C NMR (DMSO-d_6, 125 MHz), δ: 43.68, 56.10, 56.12, 111.54, 111.74, 112.34, 119.97, 120.45, 120.96, 121.39, 122.43, 123.06, 125.06, 128.35, 129.56, 132.41, 132.81, 136.12, 143.82, 152.75, 157.25, 157.95.

Compound (**3g**) ($C_{20}H_{14}Cl_2N_2$): ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 5.41 (s, 2H), 6.29 (d, 2H, $J = 8.5$ Hz), 6.68 (d, 2H, $J = 8.5$ Hz), 7.13–7.32 (m, 8H).

Compound (**3h**) ($C_{22}H_{18}Cl_2N_2$): ^{1}H NMR (DMSO-d_6, 400 MHz), δ: 2.36 (s, 3H), 2.40 (s, 3H), 5.37 (s, 2H), 6.99–7.02 (m, 2H), 7.16 (d, 2H, $J = 8.0$ Hz), 7.25 (d, 2H, $J = 8.0$ Hz), 7.58 (d, 2H, $J = 8.0$ Hz), 7.65 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz), δ: 14.5, 47.8, 119.9, 128.6, 128.9, 129.1, 129.3, 129.6, 129.8, 131.7, 133.0, 135.9, 136.0, 150.7.

Compound (**3i**) ($C_{24}H_{24}N_2$): ^{1}H NMR (DMSO-d_6, 400 MHz), δ: 1.76 (s, 6H), 2.49 (s, 6H), 5.39 (s, 2H), 7.12–7.14 (m, 4H), 7.29 (d, 2H, $J = 8.0$ Hz), 7.34–7.41 (m, 2H), 7.49 (d, 2H, J = 8.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz), δ: 20.3, 20.6, 21.1, 21.4, 48.1, 110.6, 119.6, 125.3, 125.7, 129.1, 129.3, 129.4, 129.7, 132.2, 134.5, 137.3, 139.9, 153.2.

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