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ONE-POT SYNTHESIS OF 2-ARYL-1-ARYLMETHYL-1H-1,3-BENZIMIDAZOLE DERIVATIVES USING SULFONIC ACID FUNCTIONLIZED SILICA (SiO_2-Pr-SO_3H) UNDER SOLVENT FREE CONDITIONS

Ghodsi Mohammadi Ziarani [1*], Alireza Badiei[2], Malihe Hassanzadeh[1]

[1]Department of Chemistry, Alzahra University, Tehran, Iran. Tel.-Fax: 98 21 88041344
[2]School of Chemistry, College of Science, University of Tehran, Tehran, Iran

ABSTRACT: 2-Aryl-1-arylmethyl-1H-1,3-benzimidazoles were synthesized by the reaction of *o*-phenylendiamine with different types of aromatic aldehydes in the presence of Sulfonic acid functionlized silica (SiO_2-Pr-SO_3H) as solid acid catalyst under solvent free condition at room temperature in good to excellent yields.
Keywords. Sulfonic acid functionlized silica (SiO_2-Pr-SO_3H), 1, 2-disubstitued benzimidazoles, Solvent free conditions, *o*-phenylendiamine.

INTRODUCTION

Benzimidazole and its derivatives are an important class of bioactive molecules in the field of drugs and pharmaceuticals. Most of the members of this family have wide applications in medical chemistry such as 5-lipoxygenase inhibitors (Zarrinmayerh, et. al., 1999; Valdez, et. al., 2002), factor Xa (fxa) inhibitors (Denny et. al., 1990), a treatment for interstitial cystitis (Elokdah, et. al.,1998), potential antitumor agents (Lyenger, et. al., 1996), smooth muscle cell proliferation inhibitors (Zhao, et. al., 2000). They are known for their antitumoral, antibiotic, antifungal and antibacterial properties. Indeed, these compounds are widely used in agricultural chemistry as herbicides and in the biosynthesis of chlorophylls. In addition, benzimidazoles are very important intermediates and valuable synthons used for the preparation of many organic compounds (Bai, et. al., 2001; Hasegawa, et. al., 1999 and Figge, et. al., 2002).
Despite of their pharmacological and synthetic importance, comparatively few methods for the synthesis of 2-Aryl-1-arylmethyl-1H-1,3-Benzimidazole derivatives have been reported. These methods include reaction between an *o*-phenylendiamine and two moles of aldehyde in the presence of TMSCl (Wan et. al., 2009), $Fe(ClO_4)_3$ (Oskooie, et. al., 2007), *L*-Proline (Varala, et. al., 2007), silica sulfuric acid (Salehi, et. al., 2006), K-10 (clay) (Perumal, et. al., 2004), Ionic liquids (Dabiri, et. al., 2008), $SiO_2/ZnCl_2$ (Jacob, et. al., 2009), metal hydrogen sulfates [$M(HSO_4)_n$] in water (Niknam, et. al., 2008), and Amberlite IR-120 (Sharma, et. al., 2009).

The researches continue for finding a better catalyst for the synthesis of di-substituted benzimidazole derivatives in terms of operational simplicity, economic viability, and greater selectivity. Therefore, in continuation of our studies on the application of new acid catalysts in organic synthesis (Mohammadi, et. al., 2008, 2009, 2010), here we want to explore the catalytic activity of Sulfonic acid functionlized silica (SiO_2-Pr-SO_3H) as a heterogeneous solid acid catalyst in the selective synthesis of 2-aryl-1-arylmethyl-1H-1, 3-benzimidazoles under solvent free conditions.
Sulfonic acid functionlized silica (SiO_2-Pr-SO_3H) is an efficient heterogeneous solid acid catalyst which can easily be handled and removed from the reaction mixture by simple filtration. This catalyst was used in organic synthesis (Karimi et. al., 2007, 2005; Gupa, et. al., 2007; and Mahdavinia et. al., 2009). Mono-substituted benzimidazoles were prepared using SiO_2-Pr-SO_3H in CH_2Cl_2 at room temperature (Das, et. al. 2008).

MATERIAL AND METHODS

General information

Gc-Mass analysis was performed on a Gc-Mass model: 5973 network mass selective detector, Gc 6890 egilent. IR spectra were recorded from KBr disk using a FT-IR Bruker Tensor 27 instrument. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. The ^{1}H-NMR (250MHz) was run on a Bruker DPX, 250 MHz. SiO_2 was purchased from Merck and its particle size, surface area, and average pore diameter are respectively 2-5 mm, 499 m^2/g, and 6.4 nm.

Preparation of catalyst:

Synthesis of 3-mercaptopropylsilica (MPS) and its oxidation: To 20 g of SiO_2 in dry toluene, 25 ml of (3-mercaptopropyl) trimethoxysilane was added, and the reaction mixture was heated at reflux for 24 hrs. After this period, the mixture was filtered to obtain 3-mercaptopropylsilica (MPS) which was washed with acetone and dried in air. The solid was oxidized with H_2O_2 (excess) in methanol (20 ml) for 24 h at rt and then the mixture was filtered and washed with H_2O, and acetone to obtain SiO_2-Pr-SO_3H catalyst. The modified SiO_2-Pr-SO_3H was dried and used as solid acid catalyst in the organic synthesis.
General procedure for the preparation of 2-Aryl-1-arylmethyl-1H-1,3-benzimidazoles: Silica-based sulfonic acid (0.1 g) was placed in a flask and activated at 100 ˚C under vacuum conditions for 20 min. Then the catalyst was allowed to cool to room temperature. To this catalyst, an aromatic aldehyde (2 mmol), *o*-phenylendiamine (1 mmol) was added. The mixture was stirred at rt for 1-2 h under solvent free conditions.

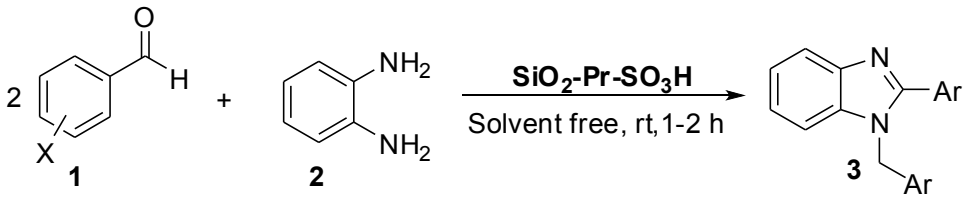
After completion of the reaction which was monitored by TLC (n-hexan/EtOAc, 3/1), the crude product was dissolved in hot ethanol, the heterogeneous solid catalyst was removed easily by simple filtration, and after cooling of the filtrate, the pure crystals of products were obtained. The acid catalyst can be reactivated by simple washing subsequently with diluted acid solution, water and acetone, and then reused without noticeable loss of reactivity.

1-(2-Hydroxybenzyl)-2-(2-hydroxyphenyl)-1H-1,3-benzimidazole **3f**: IR (KBr, cm^{-1}): ν_{max}= 3324, 3162, 2973,2871, 1595, 1456, 1397, 1244. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.81-7.84 (m, 4H), 7.13-7.43 (m, 4H), 6.77-6.93 (m, 4H), 5.64 (s, 2H), 3.70-3.78 (br, 1H), 2.64 (s, 1H). Mass (m/e): 316, 210, 182, 91, 39.

1-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)-1H-1,3-benzimidazole **3g**: IR (KBr, cm^{-1}): ν_{max}= 3045, 2997, 1607, 1588, 1513, 1377, 1258. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.78-7.87 (d, 2H), 7.69-7.73 (d, 1H), 7.54 (s, 1H), 7.15-7.41 (m, 4H), 6.65-6.90 (d, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H).

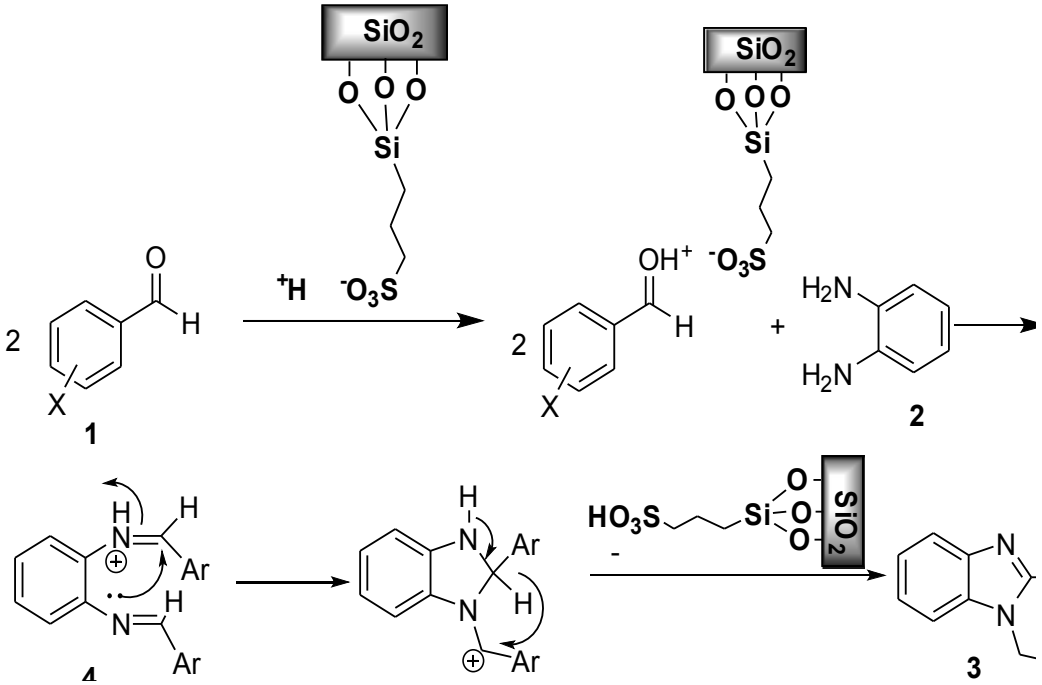
RESULT AND DISCUSSION

In the present study, all the 2-aryl-1-arylmethyl-1H-1, 3-benzimidazoles were obtained in good to excellent yields by the reaction of *o*-phenylendiamine with various aromatic aldehydes in the presence of Sulfonic acid functionlized silica (SiO_2-Pr-SO_3H) under solvent free conditions at room temperature for 1–2 h (scheme 1).



Scheme 1

The mechanism of reaction is shown in scheme 2. At first, the solid acid catalyst protonate the carbonyl group of aldehyde which then reacts with *o*-phenylenediamine to give dibenzylidene-*o*-phenylenediamine **4**. After protonation of **4** in the presence of catalyst, ring closure produces five membered ring. The deprotonation and [1, 3] hydrid transfer of intermediate give 1, 2- disubstituted benzimidazole **3**.



Scheme 2

In table1, the reaction results were reported. The various conditions were studied by carrying out the reactions under solvent free condition at different temperatures. From these results, it was decided that the room temperature is the best condition for the liquids aldehyde and the temperature of 50 °C is suitable for solid aldehydes. The reactions were completed in 1-2 hours. After completion of the reaction (monitored by TLC), the crude product was dissolved in hot ethanol, the heterogeneous solid catalyst was removed easily by simple filtration, and after cooling of the filtrate, the pure crystals of products were obtained. The acid catalyst can be reactivated by simple washing subsequently with diluted acid solution, water and acetone, and then reused without noticeable loss of reactivity. The new products were characterized by IR and NMR spectroscopy data for new compounds. Melting points are compared with reported values in literature.

As what we reported in our publications (Mohammadi, et. al. 2009), the surface of silica was first functionalized and grafted with (3-mercaptopropyl) trimethoxysilane (MPTS) (Van Rhijn, et. al., 1998) and then the thiol functionalities were then oxidized into sulfonic acid groups by hydrogen peroxide to give SiO_2-Pr-SO_3H as solid heterogeneous catalyst (scheme 3). Acid sites have been incorporated into silica surface by both grafting and co-condensation methods (Lim, et. al., 1998; Badley, et. al. 1989). The surface of the catalyst was analyzed by different method such as TGA, BET and CHN methods which were demonstrated that the organic groups (propyl sulfonic acid) were immobilized into the pores (Mohammadi, et. al. 2009).

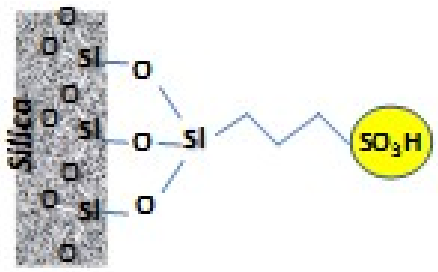
Table 1: Synthesis of 1, 2- disubstituted benzimidazoles in the presence of SiO_2-Pr-SO_3H under solvent free conditions.

Entry	Aldehyde	Product	Yield (%)	mp °C	mp °C (Lit.)
1	Ph	**3a**	90	130-132	132 (Perumal, et. al. 2004)
2	4-$OCH_3C_6H_4$	**3b**	87	129-131	131 (Perumal, et. al. 2004)
3	4-$CH_3C_6H_4$	**3c**	85	128-130	126 (Perumal, et. al. 2004)
4	4-ClC_6H_4	**3d**	95	262-265	137 (Perumal, et. al. 2004)
5	2-$OCH_3C_6H_4$	**3e**	92	149-151	151 (Perumal, et. al. 2004)
6	2-OHC_6H_4	**3f**	95	200-204	207-208 (Ravi, et. al. 2007)
7	3,4-$(OCH_3)_2C_6H_4$	**3g**	88	235-236	171-173 (Sharma, et. al. 2009)
8	4-$(CH_3)_2NC_6H_4$	**3h**	89	252-253	252 (Perumal, et. al. 2004)
9	4-$NO_2C_6H_4$	**3i**	90	191-193	192 (Perumal, et. al. 2004)
10	4-OHC_6H_4	**3j**	92	250-251	254-256 (Ravi, et. al. 2007)

The synthesis of 2-Aryl-1-arylmethyl-1H-1, 3-benzimidazoles has been studied with several catalysts in literature (Table 2). The present methodology offers several advantages such as excellent yields, a simple procedure, short reaction times, easy synthesis, simple work-up and greener conditions in contrast with other existing methods.

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

Entry	Catalyst	Condition	solvent	Yield (%)	Time	Ref.
1	Silica sulfuric acid	rt	H_2O	60-90	1-3 h	[11]
2	K-10	MW	-	87-96	10 min	[12]
3	$Fe(ClO_4)_3$	rt	-	35-93	10-20 min	[9]
4	Ionic Liquids	rt	-	80-95	1-5 h	[13]
5	TMSCl	rt	H_2O	51-92	5 h	[8]
6	Amberlite IR-120	rt	Et/H_2O (2:1)	70-95	1.45-6.5 h	[16]
7	*L*-Proline	rt	chloroform	72-95	5-8.5 h	[10]
8	SiO_2-Pr-SO_3H	rt	-	85-95	1-2 h	This work



Scheme 3

Conclusion

In conclusion, we have reported a practical and novel procedure for the synthesis of 2-aryl-1-arylmethyl-1H-1,3-benzimidazole derivatives using silica-based sulfonic acid as nano-catalyst under solvent free condition. The present method has several advantages such as operational and experimental simplicity, readily availability, easy workup procedure and high yields of products. We believe that this Silica-Based Sulfonic acid promoted methodology has a valuable contribution to the existing processes in the field of synthesis of 2-aryl-1-arylmethyl-1H-1,3-benzimidazoles.

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