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Research Article

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Nafion-H act as a Mild Efficient Reusable Catalyst for the Synthesis of 2-Substituted-1H-Benzimidazoles in solvent free condition

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ABSTRACT

2-Substituted-1H-Benzimidazole derivatives has been prepared successfully by a one pot two component condensation method of varies substituted orthophenylene diamine and varies substituted aldehydes under solvent free condition in presence of Nafion-H catalyst. Microwave heating gave excellent yield of the product within a very short reaction time compared to conventional heating. Reusability and recyclability of the catalyst was explored in the reaction.

Keywords: Green methodology; Benzimidazole; Nafion-H; Microwave heating

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INTRODUCTION

Benzimidazole derivatives are very attractive heterocyclic systems and have manifold role in organic and as well as phermacitucles chemistry1. Recently, bisbenzimidazoles shows DNA minor-groove binding agents with antitumor activity2. Benzimidazole derivatives are widely used against several diseases such as anticancer, antifunga, antimicrobial5, anti-inflammatory, antihistaminic and antiviral properties such as influenza, Herpes (HSV-1)9. It has an ability to bind with transition metals for modeling biological chemistry [1]. It was also found that Vitamin B12 possesses the core benzimidazole moiety.

MATERIALS AND METHODS

Therefore benzimidazole derivative synthesis gets more attention in recent years. Benzimidazole derivatives were synthesized in various processes by the condensation between carboxylic acid or derivatives (nitriles, imidates, or orthoesters) and orthophenylenediammine in different conditions. Various homogeneous catalyst usually strong acid like PPA, mineral acid, HCl, p-TSA, p-TsOH16, SSA, weak acid like boric acid7 Dowex50W and Lewis acid such as BE3.OEt219, In(OTf)3 19b heterogeneous catalyst like KSF clay, HBF4-SiO221, SiO_2-FeCl322 have been used

to perform this reaction. In addition, several ionic liquids23, solvent free microwave irradiation, 24 towards the synthesis of benzimidazoles have been employed. In the alternative approach benzimidazole have been prepared from o-phenylene diamine and substituted benzaldehyde in presence of catalyst such as Ruthenium (II)25, TiCl3OTf26 ,VOSO427 , Yb(OTf)328, sodium perborate 29, MgCl2•6H2O30 , B(C6F5)331 were reported in recent years. However, some of these processes were associated with drawbacks such as a hazardous solvents, Strong acid condition, multi-step procedure, drastic reaction conditions, laborious experimental procedure, long reaction times, and low yields. It is therefore important to find more convenient rapid method for the preparation of Benzimidazole derivatives. In current year's insoluble, highly stable, recoverable and recyclable solid perfluorinated resin-supported sulfonic acid (Nafion-H) was found to be a suitable heterogeneous catalyst in organic synthesis such as in acylation32, alkylation33, acetal synthesis34, Diels Alder 35 and nitration36 reactions. In recent years conventional heating method is replaced by microwave oven irradiation because it has the following advantages such as (a) gas burner flame is not required for high temperature, (b) it reduces reaction time, (c) low quantity of reagents are required which is good for environment, (d) energy saving method that means greater % of energy reaches to the reactant. Thus, Nafion-H was chosen for the condensation reaction for benzimidazole derivative synthesis in one pot method under microwave heating conditions [2].

RESULTS AND DISCUSSIONS

Here, I report a clean and single-step two component reactions of Orthophenyldiammine 1, aromatic aldehydes 2 (Figure 1) in presence of catalytic amount Nafion-H under solvent free condition with good yields.

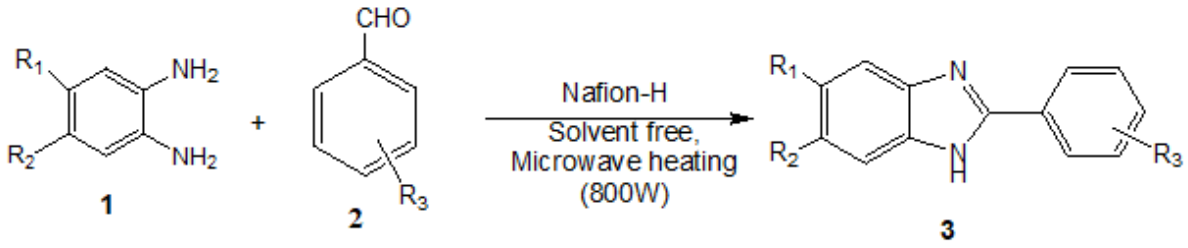

Figure 1: Synthesis of 2-substituted-1H-benzimidazoles catalysed by Nafion H under solvent free condition

In this context, I examined the synthesis of various benzimidazole derivatives in presence of different mol percent of catalyst under different conditions. To explore the synthetic applicability of the catalyst towards the synthesis of a variety of benzimidazoloes I carried out an opening examination with 4-chlorobenzaldehyde (1 mmol) and orthophenylene diamine (1.2 mmol) as a substrate and reagent in conventional heating and also microwave heating separately. The various reaction conditions have been examined for the synthesis of 2-(4′-chlorophenyl)-1H-benzimidazole and the result of the optimization reactions are found that the reaction proceeded best in presence of

10 mol % of catalyst under solvent free medium in microwave heating condition (Table 1). Furthermore to discuss the effect of catalytic activity, I carried out a string of reactions with increasing amount of catalyst. It was observed that with increasing the amount catalyst beyond 10 mol % showed no considerable development of yield and reaction time in both heating methods (Table 1, Entry no 6,7,8,9). 90% yield of the desired product was obtained in microwave heating condition with 10 mol % of catalyst against 75% yield in conventional heating in oil bath at 1200°C. It was observed that low yield was obtained if less than 800W powers in microwave oven were applied. At 1200W the yield was very low and it can be attributed due to loss of starting materials by charring. Similar observation was recorded when the reaction was heated at 1400C in an oil bath. So I can finally conclude that microwave heating gave better result than conventional heating method clearly represented in Figure 1. After the optization of the mol % of the catalyst then different solvent effects were investigated (Table 2). The reaction was carried out in solvents such as H2O, EtOH, DMF, acetonitrile, THF. However in all solvent % isolated yield was moderate and solvent free condition was established to be the best condition for this reaction (Table 2).

Table 1: Study of the catalytic activity of the catalyst in different heating methods

Entry No	**Nafion- H (mol %)**	**Solvent**	**A Conventional heating**	**A Yield (%)**	**B Microwave heating**	**B Yield (%)**
1	0	Free	Oil bath 90°C, 6hrs	10	800W,15mins	15
2	5	Free	Oil bath 90°C, 6hrs	25	800W,15mins	50
3	10	Free	Oil bath 90°C, 6hrs	45	800W,10mins	90
4	10	Free	Oil bath 120°C, 6hrs	75	800W,10mins	90
5	10	Free	Oil bath 140°C, 6hrs	56	1200W,10mins	60
6	15	Free	Oil bath 90°C, 6hrs	72	800W,10mins	90
7	15	Free	Oil bath 120°C, 6hrs	75	800W,10mins	90
8	20	Free	Oil bath 90°C, 6hrs	75	800W,10mins	90
9	20	Free	Oil bath 120°C, 6hrs	75	800W,10mins	90
Reaction condition: P-chlorobenzaldehyde (1mmol) and orthophenylenediammine (1.2 mmol) in different mol% of catalyst (Nafion H)						

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Table 2: Study of the solvent effect in this reaction

Entry No	Nafion H (mol %)	Solvent (2 mL)	A Conventional heating	A Yield (%)	B Microwave heating	B Yield (%)
1	10	H_2O	Oil bath 1200C,reflux 6hrs/8hrs	70/72	800W,10/15mins	55/60
2	10	DMF	Oil bath 1200C, 6hrs/8hrs	45/46	800W,10/15mins	52/60
3	10	EtOH	Oil bath 1200C, 6hrs/8hrs	72/70	800W,10/15mins	56/58
4	10	MeCN	Oil bath 1200C, 6hrs/8hrs	46/50	800W,10/15mins	56/58
5	10	THF	Oil bath 1200C, 6hrs/8hrs	40/42	800W,10/15mins	50/62
6	10	Solvent free	Oil bath 1200C, 6hrs	75	800W,10mins	90
Reaction condition: P-chlorobenzaldehyde (1mmol) and orthophenylenediammine (1.2 mmol) in 10 mol% of Nafion H catalyst						

After developing the optimization of the reaction conditions the generality and scope of the substrate for the described method were developed by using four different ophenylenediamines and varies aldehydes. A series of benzimidazoles have been synthesized by using several aldehydes, such as aromatic and heteroaromatic bearing donating and withdrawing groups provided the corresponding 2-substituted-1H-benzimidazoles in 78-90% yield in short reaction times (Table 3). In the present method methoxy, halogens, cyano, methyl groups did not affect the yield of the reaction. I studied the reusability of the catalyst Nafion-H for the synthesis of 2-(4′-chlorophenyl)-1H-benzimidazole.

It was also observed that electron electron-withdrawing groups containing aldehydes gave the better yield of the product rather than the electron-donating group containing aldehydes but yield of the reaction did not depend on the reactivity of the o-phenylenediamine because nucleophilic addition reaction depends on the reactivity of the aldehyde only. I expect that strong electron-withdrawing groups on aromatic ring such as p-nitrobenzaldehyde gave the better yield of the product (3m) but it took larger reaction time to generate 82% yield [3].

Table 3: Synthesis of various 2-substituted-1H-benzimidazoles in presence of Nafion-H catalyst (10 mol%) under solvent free condition

Entry No	O-phenylene diammine [1]		Aldehyde (R_3) [2]	Product [3]	Time (mins)	Yield (%)	MP (^{0}C)	
	R_1	R_2					Found	Reportd
1	H	H	4-OH	3a	14	80	234	234-236
2	H	H	4-Me	3b	12	85	266	265-269
3	H	H	4-Cl	3c	10	90	302	303-304
4	H	H	2-OMe	3d	10	85	156	156-158
5	H	H	2-NO_2	3e	12	86	262	261-263
6	H	H	4-OMe	3f	12	82	224	225
7	H	H	4-CN	3g	10	85	264	260-262
8	H	H	4-NO_2	3h	12	82	310	308-310
9	H	H	H	3i	8	85	302	302-303
10	H	H	4-Br	3j	10	86	298	298-300
11	H	H	2-Furanyl	3k	8	78	286	286
12	Me	Me	4-Cl	3l	10	88	260	262
13	Me	Me	4-CN	3m	10	85	199	198-200
14	Me	Me	2,5$(OMe)_2$	3n	10	82	270	272-274
15	COPh	H	4-OMe	3o	15	83	180	180-182
16	COPh	H	4-CN	3p	14	84	236	238-240
17	Cl	Cl	4-CN	3q	14	82	>320	>320
18	Cl	Cl	4-Br	3r	12	82	285	285

The effectivity of different catalysts in the synthesis of 2-(4′-chlorophenyl)-1H-benzimidazole has been compared with some previously published papers in Table 4. The shorter reaction time and also high yield confirms the high efficiency of the Nafion-H heterogeneous catalyst in this reaction.

A plausible reaction mechanism and the catalytic role of Nafion-H were presented in Scheme 2. In this methodology, Nafion H acts as a Brønsted acid and plays a significant role to increase the electrophilicy of the carbonyl oxygen by protonation at the oxygen centre there by nucleophilic attack to carbonyl carbon took place rapidly which increased the overall rate of the reaction. Mechanism may proceed through the imines form proved in earlier papers and then cyclisation followed by oxidation produces the desired product. After the completion of the reaction then reaction mixture was cooled and ethyl alcohol was added into it and then filtered. Then filtrate was concentrated and dried in vacuum. Then it was reused up to three times under the same reaction conditions. The recovered Nafion-H catalyst showed good activity with slight decrease of its efficacy over three runs. It was clearly depicted.

The following benefits of this method come from discussion are (a) Solvent free medium was successfully applied to preserve Eco friendly reaction medium; (b) The catalytic method was explored in this reaction; (c) Yields are obtained in very Short reaction time; (d) Cheap and simple procedure had been used for workup process; (e) Hazardous solvents were not used for purification of the product; (f) Catalyst was reused for three times in the reactions without loss of its efficacy.

All chemicals and solvents are used AR grade. All aromatic aldehydes, o-phenylenediamine were purchased from Spectrochem, Pvt. Ltd. Mumbai, India. Nafion-H was collected from my PhD supervisor. 1H and 13C NMR spectra were recorded on Bruker 300 MHz spectrometer using Tetra Methyl Silane (TMS) as an internal standard and CDCl3 and DMSO-d6 are used as solvents. IR spectra were recorded on a Perkin-Elmer spectrometer as KBr disc. Organic solvent was dried with Magnesium sulfate. Melting points were measured with apparatus. Reactions were monitored by Thin-Layer Chromatography (TLC) on glass sheets pre-coated with silica gel [4].

General Procedure for the synthesis of 2-substituted-1H-benzimidazoles: A mixture of 4-chlorobenzaldehyde (1mmol, entry 3, Table 3) with orthophenylene diammine (1.2 mmol, 1a), Nafion-H (10 mol %) were mixed in a 50 mL conical flask and it was heated in microwave oven with power 800W. The reaction was monitored by TLC. A brown spot was developed in an iodine chamber within 8-15 mins. Then the crude product was cooled and diluted with ethylacetate, and filtered. The filtrate was washed two times with 30 mL saturated aqueous bicarbonate solution. It was washed three times with 30mL brine solution. Then it was concentrated in a rotary evaporator under vacuum. The product was crystallized directly from hot aqueous ethanol to produce the pure 2-substituted benzimidazoles with 78-90% yield. All the known compounds were characterized by comparing their physical and spectral data with authentic compounds [5].

CONCLUSION

I have developed a new highly efficient and improved green methodology for the synthesis of a wide variety of 2-substituted-1H-benzimidazoles using available, nontoxic catalyst under solvent free condition. A series of 2-substituted-1H-benzimidazoles were developed with varies aromatic aldehydes and varies o-phenylenediamine under mild reaction conditions with excellent yield. Microwave heating, solvent free technique, easy purification of

the isolated products (no need of column chromatography) in the reaction is the main advantages of this process. I therefore hope that this green methodology would be more beneficial to both academia and industrial process.

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