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Preparation and Characterization of New Heterogeneous Catalyst Polymer-Supported Reagent and its Application in the Green Synthesis of 2-Substituted Benzimidazoles

Jagnnath S. Jadhav, Rajanikant M. Kurane, Babasaheb D. Ajalkar, Kanchan S. Joshi-Kulkarni*
Department of Chemistry, Shivraj College, Gadhinglaj, Maharashtra, India

ABSTRACT A polymer-supported reagent (PSR) was synthesized by exploiting the propensity of Merrifield resin to undergo quaternization with 1-*N*-methylimidazole followed by anion metathesis reaction. The characterization of PSR was also made by various techniques including Fourier transform infrared, ^{13}CNMR, ^{1}HNMR, Scanning electron micrographs, and thermogravimetric analysis. The PSR was effectively employed in the synthesis of 2-substituted benzimidazole derivatives. Benzimidazole derivatives (**3a-k**) were synthesized by the reaction of *o*-phenylenediamine (**1**) with aryl aldehydes (**2**) in the presence of PSR. The development of new solid-phase reagent is beneficial for offering easy purification, selectivity, recycling, and green protocol.

KEYWORDS Benzimidazole, Heterogeneous catalyst, o-Phenylenediamine, Polymer-supported reagent.

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INTRODUCTION

Development of a highly efficient and robust new solid-phase reagent is a subject of great interest for the synthesis of organic molecules, which leads to biologically active compounds and also for the optimization of drug candidates.[1] First time, Professor Bruce Merrifield in 1963 introduced solid-phase reagent as heterogeneous catalyst using vinyl benzoic acid-based resin by exploitation.[2] To develop new and improved strategies for preparation of novel heterogeneous catalyst which is the demand of recent years to meet approximate environmental standards for greening of chemistry. A number of advantages arise by the use of solid-phase reagent mainly ease of purification process after reaction facilitating significant advances in selectivity, recycling, reproducibility, and activity.[3] At the same time, they can add economic value through more efficient consumption of energy through the use of milder conditions and greater atom economy by reducing the steps.[4] The development of functional polymer based on Merrifield resin provides significant stability to mechanical, chemical, and thermal demands on the diverse operating conditions.[5] To develop new and improved strategies is the demand of recent years for the synthesis of organic compounds using new robust heterogeneous catalyst based on Merrifield resin.[6] Although the reaction has been investigated using Lewis and Bronsted acid catalyst, there is a scope for improvement especially toward developing a new protocol using highly efficient and reusable catalyst.[7-14]

Heterocyclic compounds play a significant role in human life. Benzimidazoles and its derivatives are important heterocyclic compounds in the field of drugs and pharmaceuticals. Benzimidazole derivatives represent most biological active class of compounds possessing a wide spectrum of activity which are well documented in literature. Benzimidazole ring is a useful synthon in medicinal chemistry and is a part of many biological compounds such

*Corresponding author: Email: rajanikantkurane@gmail.com

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as purine in DNA and Vitamin B_{12}[15]. Nowadays, infectious microbial diseases are causing problems worldwide. Hence, there will be a vital need to discover chemotherapeutic agents and benzimidazole derivatives remain a main focus in medicinal research. Derivatives of benzimidazole are widely used as anticancer,[16] bactericidal,[17] anti-viral,[18] HIV infectivity,[19] analgesics, etc. Moreover, 2-substituted benzimidazole derivatives are valuable synthons that can be used in preparation of other fused ring compounds such as triazolo-, oxazino-, or furino-benzimidazole derivatives. Various reagents employed for the construction of benzimidazoles include concentrated HCl,[20] NH_4Cl,[21] $Na_2S_2O_5$,[22] $LaCl_3$,[23] $In(OTf)_3$,[24] Na_3AlF_6,[25] dioxane dibromide,[26] $Zn(OTf)_2$,[27] blue light-emitting diodes and molecular oxygen,[28] $Ni(OAc)_2$,[29] and sodium dodecyl sulfate.[30]

As a part of our on-going investigation related to polymer-supported reagent (PSR),[31] we report herein a new method for construction of 2-substituted benzimidazoles using polymer-supported catalyst.

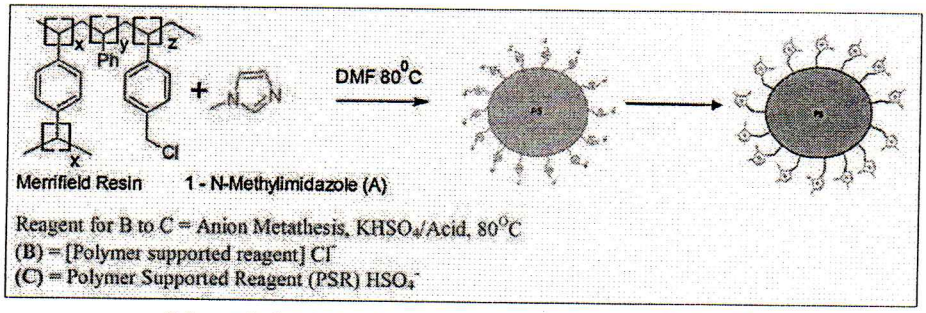
RESULTS AND DISCUSSION

In the synthesis of PSR **[Scheme 1]**, Merrifield resin was quaternized with 1-*N*-methylimidazole (**A**) to give [PSR] Cl^- (**B**). The resulting compound when treated with excess amount of $KHSO_4$ underwent anion metathesis reaction to afford the desired (PSR) HSO^-_4 (**C**). The Fourier-transform infrared (FT-IR) and FT-Raman spectroscopy were performed to monitor the progress of the reactions involved in the synthesis of **C**. The reaction of **A** with Merrifield resin was supervised using FT-Raman spectroscopy. The negative bands at 640 cm^{-1} (C-Cl stretching band) and 1267 cm^{-1} (waging bands of CH_2-Cl) almost disappeared while the peaks at 615.93 cm^{-1} (Me-Cp stretching band), 1166.25 cm^{-1}, 1335 cm^{-1}, 1408 cm^{-1}, and 1445.08 cm^{-1} (ring stretching mode of imidazolium ring), 3064.45 cm^{-1} and 3135 cm^{-1} (C-H stretching of Cp rings) increased in intensity after 72 h reflecting the substantial grafting of **A** in matrix of Merrifield resin. Anion metathesis reaction was monitored using FT-IR spectroscopy. Appearance of peaks at 615.93 cm^{-1}, 695.04 cm^{-1}, 753.49 cm^{-1}, and 828.20 cm^{-1} which are characteristic of HSO^-_4 confirmed the formation of **C**. The HSO_4^- loading of the PSR as determined by EDAX was found to be 0.1323 mmole of $HSO^-_4\,g^{-1}$.

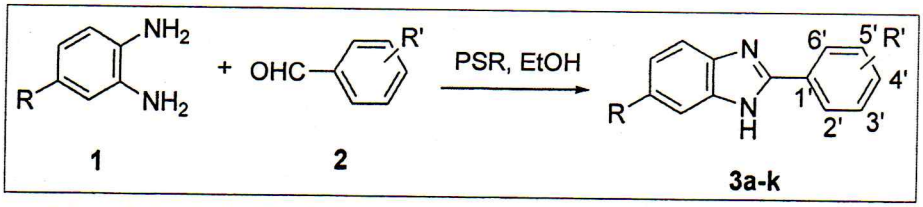
Scanning electron micrographs at various stages of **C** were recorded to understand the morphological changes occurring on the surface of Merrifield resins. Scanning was done across the length of polymer beads. Comparison of images taken at a magnification of ~5 × 10^2 indicates that the spherical beads of Merrifield resin with smooth surface **[Figure 1a]** were altered on functionalization. The resin beads in **C** were not spherical like original Merrifield resin beads **[Figure 1b]**. In fact, the bead degradation occurred **[Figure 1b]** was plausibly due to the stress generated during the surface confinement of the Merrifield resin with **A** and the subsequent anion metathesis reaction.

Thermogravimetric analysis revealed that the Merrifield resin as well as **C** degraded in two stages **[Figure 2]**. The former began to decompose at 400°C and lost almost all mass at 800°C while the latter which contained about 15% evaporable moieties such as physisorbed water and volatile solvents occluded during handling started to decompose at 300°C and lost most of its mass at 615°C. The profiles of thermogram manifested that **C** was comparatively less stable than the Merrifield resin.

Our next task was to assess the catalytic activity of **C** in the synthesis of 2-substituted benzimidazole derivatives **[Scheme 2]**. Initial studies started with the reaction *o*-phenylenediamine (**1**, R = H) with benzaldehyde (**2**, R = H) using 50 mg of PSR in solvent EtOH at room temperature **[Table 1, entry 3]**. The reaction was completed in 45 min as confirmed by thin-layer chromatography (TLC). The reaction mixture was poured into ethyl alcohol and extracted with ethyl acetate. The desired product,



Scheme 1: Synthesis of polymer-supported reagent HSO_4^- (C)



Scheme 2: Synthesis of 2-substituted benzimidazoles using polymer-supported reagent

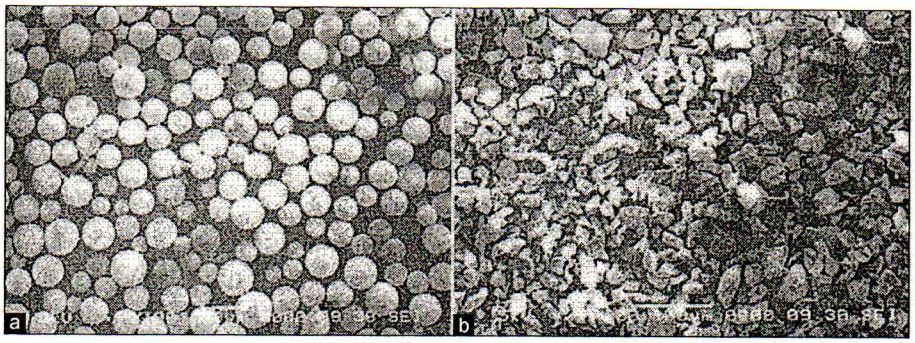


Figure 1: Scanning electron micrographs (images) of (a) Merrifield resin and (b) polymer-supported reagent catalyst.

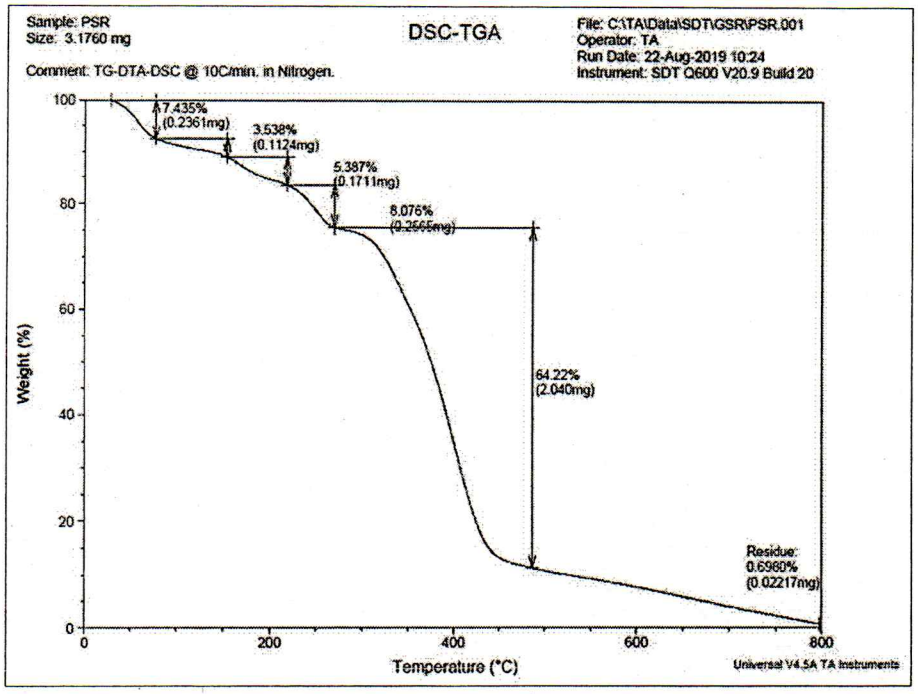


Figure 2: Polymer-supported reagent-thermogravimetric analysis

Table 1: Effect of amount of catalyst on model reaction (formation of 3a)

Entry	Amount of catalyst in g	Time (min)	Yield (%) of 3a
1	0.000	60	No
2	0.025	55	50
3	0.050	45	70
4	0.100	40	93
5	0.125	25	88
6	0.150	25	88
7	0.200	20	91

2-phenylbenzimidazole (**3a**), was obtained in 70% yield. A parallel experiment was also carried to confirm that no product was obtained in the absence of **C**.

Next, we investigated catalyst loading on the synthesis of 2-substituted benzimidazole compounds **[Table 1]**. No product was formed in the absence of catalyst, whereas yield was maximum when 0.1 g PSR was used **[Table 1, entries 1–4]**. However, on further increase in the amount of catalyst, there was no detectable change in the yield. Thus, 0.1 g PSR, using EtOH solvent at room temperature, gave the best results.

We also investigated the influence of solvent on the outcome of the aforementioned synthesis of 2-substituted benzimidazole reactions catalyzed by polymer-supported catalyst **[Table 2]**. It was observed that ethanol was effective in providing higher conversion **[Table 2, entry 4]**, whereas chlorinated solvents such as $CHCl_3$ and CH_2Cl_2 **[Table 2; entry 1, 2]**, in protic solvents such as MeOH and H_2O **[Table 2; entry 3, 5]**, and in protic solvents such as CH_3CN, tetrahydrofuran, dimethylformamide (DMF), and toluene **[Table 2; entry 6–9]** showed lower conversion of desired product. Therefore, we optimized the reaction and chose green solvent ethanol for our synthesis.

With optimization condition in hand, we evaluated the scope of structurally diverse aryl aldehydes in the presence

of **C** [**Scheme 2**] and results are summarized in **Table 3**. A variety of aldehyde having electron-withdrawing as well as electron-donating substituents reacted efficiently affording products with high yield. It was observed that aldehydes having electron-withdrawing group afford better yields with shorter reaction time as compared to aldehydes with electron-donating group [**Table 3**]. It is reasonable to assume that the significant improvement in the catalytic activity of **C** may stem from HSO_4^- tagged that enhances micropolarity and a key factor for the catalyst-like PSR.

The successful recovery and reuse of catalyst is an essential aspect of green chemistry and is one of the important factors in determining its potential value for large-scale operation and industrial point of view. To check the possibility of the catalyst recycling, the synthesis of 2-substituted benzimidazoles was carried out in the presence of **C**. After the reaction, the catalyst was separated by simple filtration, washed with DMF and dried in vacuum before being reused in subsequent runs. The catalyst could be at least used 5 times without noticeable decrease in catalytic activity [**Figure 3**]. The FT-IR and FT-Raman were indistinguishable from those of the fresh catalyst, which revealed that the main characteristics of the catalyst were preserved during recycling and reuse.

EXPERIMENTAL SECTION

General

All chemicals and solvents were purchased from Aldrich and Sigma Company and used without further purification. The melting points of the compounds were recorded by open capillary apparatus and were uncorrected. Column chromatography was carried on silica gel of 60–120 mesh size. IR spectra of compounds were obtained on a PerkinElmer, FT-IR spectrophotometer with substances being pressed in a KBr pellet. The ^{1}HNMR and ^{13}CNMR spectra of sample were recorded on a Bruker Spectrometer at 300 MHz and 75 MHz, respectively, using $CDCl_3$ as solvents and tetramethylsilane (TMS, δ = 0ppm) as an internal standard. Chemical shifts of proton were reported in ppm down field from TMS. Coupling constants are reported in Hertz (Hz). The C.H.N elemental analysis was performed on EURO EA3000 vector model.

Preparation of polymer-supported catalyst

Preparation of [PSR]Cl^-(**B**): A mixture of Merrifield resin (3.0g) and 1-N-methylimidazole (**A**) (2.0 mL) in 25 mL of DMF was heated at 80°C in an oil bath for 72 h. The [PSR] Cl^- was filtered, washed with DMF (3 × 50 mL), MeOH (3 × 50 mL), and CH_2Cl_2 (3 × 50 mL), and dried under vacuum at 50°C for 24 h to afford [PSR]Cl^-(**B**).

Elemental analysis: %C 42.91, %H 3.86, and %N 3.97. Loading 1.54 mmol of functional group g^{-1} resin.

Preparation of [PSR]HSO_4^- (**C**): A suspension of [PSR]Cl^- (3.0 g) in 25 mL DMF was stirred under a stream of nitrogen gas while being cooled in an ice bath, $KHSO_4$ (3 mmol) was added in small portion and stirred the suspension. The whole quantity of $KHSO_4$ was added to the reaction mixture and the system was heated at 70°C for 72 h. Afterward, polymer-supported catalyst filtered and washed with DMF (3 × 20 mL), MeOH (3 × 20 mL), MeOH:H_2O (1:1) (3 × 20 mL each). The catalyst was dried under vacuum in 50°C for 48 h to afford [PSR]HSO_4^- (**C**). FT-IR: - υ = 3740.28, 1699.51, 1651.38, 1445.08, 1367.56, 1156.25, 1050.0, 805.0, 748.0, 656.0, 543.0, and 437.0 cm^{-1}. Raman: - υ = 1335, 1658, 1478, 1408, 1327, 1251, 828.20, 753.49, 695.04, and 615.93 cm^{-1}; loading: 1.323 mmol of HSO_4^- per gm resin.

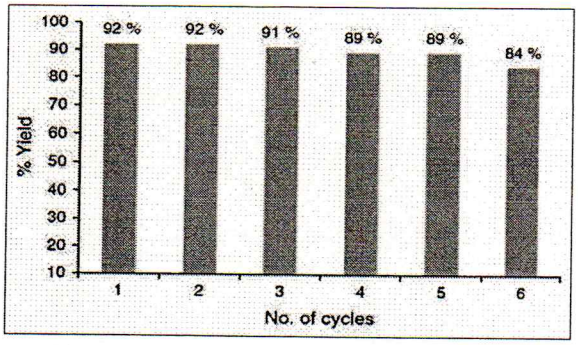


Figure 3: Recyclability and reusability of catalyst

Table 2: Effect of solvent on model reaction (3a)

Entry	Solvent	Yield (%)
1	$CHCl_3$	56
2	CH_2Cl_2	60
3	MeOH	72
4	EtOH	94
5	H_2O	29
6	CH_3CN	46
7	Tetrahydrofuran	44
8	Dimethylformamide	51
9	Toluene	67

Table 3: Synthesis of 2-substituted benzimidazoles (3a-k) according to Scheme 2

Product 3	R	R'	Time min	Yield (%) of 3	Mp (°C) [ref]
a	H	H	40	93	296[32]
b	H	4'-Cl	25	97	290[35]
c	H	2'-Cl	20	93	234–238[36]
d	H	3'-NO_2	30	93	200–202[34]
e	H	4'-NO_2	35	96	300–308[34]
f	H	4'-OH	20	84	271[33]
g	H	4'-OMe	25	82	224–225[34]
h	H	4'-Me	35	78	278[33]
i	H	4'-Br	30	96	299[36]
j	H	2',4'-Cl_2	25	91	246[36]
k	Me	4'-NO_2	25	98	308-310[34]

General procedure for the synthesis of 2-substituted benzimidazole derivatives

A mixture of *o*-phenylenediamine (1.0 mmol), aromatic aldehydes 1.2 mmol), and 3 mL ethyl alcohol under open

oxygen in the presence of 100 mg of PSR catalyst was stirred at room temperature. The reaction was monitored by TLC, diluted with ethyl alcohol (15 mL) and catalyst PSR was separated by filtration. The solvent was removed under reduced pressure and crude product was subjected to column chromatography using petroleum ether/ethyl acetate (v/v 90:10).

Characterization data of representative compounds

2-(4'-Chlorophenyl)-1*H*-benzo[d]imidazole (**3b**): Colorless solid. Yield 97%. m.p. 290–92°C. IR (KBr): 3038, 1440, 1410, 1268, 950, 754 cm^{-1}; NMR (500 MHz, DMSO-d_6): δ 12.9 (s, 1H, NH), 8.15 (d, 2H), 7.49–7.64 (m, 4H), 7.20 (m, 2H); NMR (100 MHz, DMSO-d_6): δ 111.1, 118.6, 121.9, 126.2, 128.6, 129.5, 130.0. 134.8, 143.5, 151.0; ESI-MS: Calcd. m/z 194 and Obsd. m/z 193.

2-(3'-Nitrophenyl)-1*H*-benzo[d]imidazole (**3d**): Dirty white solid. Yield 93%. m.p. 200–202°C.IR (KBr): 3040, 1441, 1370, 1262, 966, 734 cm^{-1}; HNMR (500 MHz, DMSO-d_6): δ 13.28 (s, 1H, NH), 9.0 (s, 1H), 8.55 (d, 1H), 8.34 (d, IH), 8.3 (m, 1H), 7.5–7.8 (dd, 2H), 7.24 (t, 2H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 111.6, 119.1, 119.6, 120.7, 122.1, 123.2, 124.1, 130.6, 131.6, 135.2, 143.5, 148.3, 149.0; ESI-MS: Calcd. m/z 239.22 and Obsd. m/z 240.07.

2-(4'-Methoxyphenyl)-1*H*-benzo[d]imidazole (**3g**): Pale yellow solid. Yield 82%. m.p. 224–225°C;^{1}HNMR (500 MHz, DMSO-d_6): δ 12.72 (s, 1H, NH), 8.08 (d, 2H), 7.13 (s, 2H), 7.07 (m, 4H), 3.80 (s, 3H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 55.85, 114.1, 122.0, 123.2, 128.5, 129.5, 151.8 and 161.1; ESI-MS: Calcd. m/z 224.25 and Obsd. m/z 225.13.

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