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PMA/SiO_2: An efficient synthesis of 2-substituted 1,3-benzazoles by green approach

V. Sinivas Goud and Monalisa Boruah

Department of Chemistry, Shri Jagadish Prasad Jhabarmal Tibrewala University, Vidyanagari, Jhunjhunu, Rajasthan

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ABSTRACT

A mild, efficient and an eco-friendly method is described to synthesis of 1,3-benzazole by Phosphomolybdic acid supported on silica gel (PMA/SiO_2) facilitated reaction of 1,2-phenylenediamine / 2-aminothiophenol with alkyl/aryl aldehydes with excellent yield. A variety of benzazoles derivatives were prepared by using this green methodology in good yields and PMA/SiO_2 was found to be an inexpensive and reusable catalyst.

Keyword: PMA/SiO_2, 1,3-benzazoles, PEG-400, green chemistry

INTRODUCTION

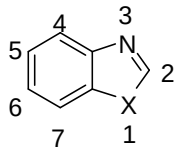
Development of efficient and environmentally friendly synthetic methodologies for the commonly used small organic molecules is one of the major challenges in modern organic synthesis. Synthesis of 1,3-Benzazoles (**A**, Figure 1), a very important class of heterocyclic compounds (benzimidazole and benzothiazole) as considered as privileged structures in the biologically active [1], has given more attention of the Organic chemist due its wide application in pharmaceutical field. Drugs displaying 1,3-Benzazoles ring include proton-pump inhibitors (Omeprazole (**B**) Figure 1), AT1 receptor antagonists (Telmisartan (**C**) Figure 1), direct thrombin inhibitor (Dabigatran (**D**) Figure 1), treatment of amyotrophic lateral sclerosis Riluzole (**E**)and H1 receptor antagonist mizolastin (**F**) (Figure 1).

The most commonly used synthetic method to access benzimidazole consists in the condensation of 1,2-phenylenediamines with carboxylic acids[2-4] and their derivatives. [5-8] The second route involves condensation of 1,2-phenylenediamine and aldehydes followed by oxidative cyclodehydrogenation. [9-12] Coming to the construction of the 2-substituted benzothiazoles can be synthesized, [13-15] through (i) condensation–dehydration of 2-aminothiophenol with carboxylic acids, [16,17] (ii) condensation with aldehydes under oxidative conditions. [18] Although these methods are quite acceptable, however, often involve the use of various acids or reagents that are not environmentally compatible, produce a large amount of waste and require longer reaction times, higher temperatures and expensive reagents. In some of these cases the formation of side products e.g. 1,2-disubstituted benzimidazole along with the desired 2-substituted derivative were also observed.

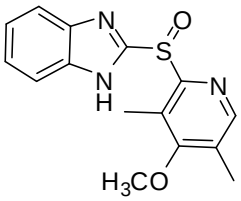
Heterogeneous catalysts are gained much importance in recent years due to economic and environmental benefits [18,19]. Recently, the use of heteropolyacids (HPAs), as environmentally friendly and economically viable solid acids are increasing continuously owing to their ease of handling and high catalytic activities. Among them

phosphomolybdic acid (PMA, $H_3PMO_{12}O_{40}$) is one of the less expensive and commercially available catalysts. [20,21]

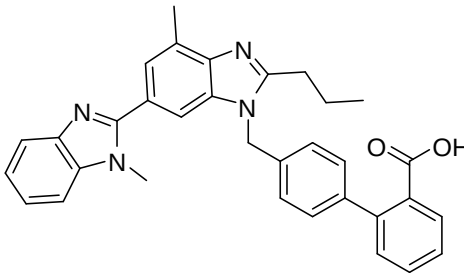
To the best of our knowledge, for the synthesis of 1,3-benzazole, the Phosphomolybdic acid supported on silica gel (PMA/SiO_2) catalysed reaction was not explored. PMA/SiO_2 is a less expensive, reusable and green catalyst. Herein, we wish to describe a new efficient and eco-friendly method to synthesis of 1,3-benzazole by PMA/SiO_2 catalyzed reaction of 1,2-phenylenediamine and benzaldehyde (Scheme-1) in presence of PEG-400 with excellent yield.



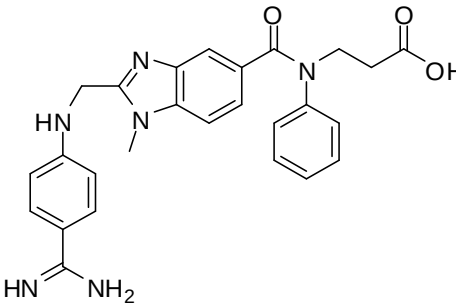
1,3-Benzazoles (**A**)
(X=N benzimidazole,
X=S benzothiazole)



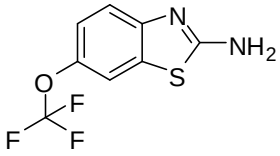
Omeprazole (**B**)



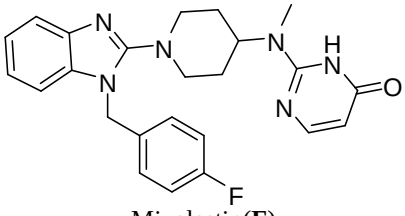
Telmisartan (**C**)



Dabigatran (**D**)



Riluzole (**E**)



Mizolastin(**F**)

MATERIALS AND METHODS

Melting points are uncorrected and were obtained in open capillary tubes in sulphuric acid bath. TLC checking was done on plastic sheets coated with silica gel GF-254 (Merck). Flash column chromatography was performed over silica gel (mesh 230–400) and hexane/ethyl acetate combination was used as the eluent. ^{1}H NMR and ^{13}C NMR spectra were determined in DMSO-d_6 solution by using 400 or 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. IR spectra were recorded using Perkin-Elmer model 1700 instrument in KBr phase. MS spectra were obtained on a mass spectrometer.

General procedure for the preparation of compound (3)
A mixture of 1,2-phenylenediamine or 2-aminobenzenethiol **1** (1 mmol), adehyde **2** (1 mmol) and PMA-SiO_2 (15 mol%) in PEG-400 (5 ml) was stirred at 75 °C for 7 hr. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature and mixturewas diluted with Et_2O. The catalyst, i.e. PMA–SiO_2 was recovered by simple filtration and crude product was purified by column chromatography on silica gel using ethyl acetate/hexane to give the desired product. The filtered catalyst was reused without drying.

2-(4-(Trifluoromethyl)phenyl)-1*H*-benzo[*d*]imidazole (3a)
White solid; mp 260-262 °C (lit[22] 262-264 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.20 (bs, 1H), 8.40 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.25-7.18 (m, 2H); IR (KBr): 3450, 1466, 1340, 1200, 1155 cm^{-1}.

4-(1*H*-Benzo[*d*]imidazol-2-yl)benzoic acid (3b)
White solid, mp 329-331 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.19 (bs, 1H), 13.02 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.25-7.21 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 167.0, 150.5, 134.8, 134.0, 131.8, 130.0 (2C), 129.6, 129.8 (2C), 129.6, 129.4, 126.6 (2C); IR (KBr): 3061, 2920, 1700, 1380, 1290, 1110 cm^{-1}; MS (ESI): m/z ([M+H]+): 239.1.

4-(1*H*-Benzo[*d*]imidazol-2-yl)-*N*,*N*-dimethylaniline (3c)
Yellow solid; mp 285-286 °C (lit[23] 288-290 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.5 (brs, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.67-7.51 (m, 2H), 7.14-7.08 (m, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 2.99 (s, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 151.8, 150.7, 139.1 (2C), 127.3 (2C), 120.8 (2C), 116.7 (3C), 111.3 (2C), 39.1 (2C); IR (KBr): 3418, 3053, 1610, 1508, 1439, 1372, 1203, 819, 747 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{16}N_3$ $(M+H)^+$ 238.1344, found 238.1340; MS (ESI): m/z ([M+H]+): 238.2.

2-(4-(Tert-butyl)phenyl)-1*H*-benzo[*d*]imidazole (3d)
White solid; mp 253-255 °C (lit[24] 250-251°C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.82 (s, 1H), 8.22 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.22-7.16 (m, 2H), 1.35 (s, 9H); IR (KBr): 3705, 2922, 1455, 1272, 955 cm^{-1}. MS (ESI): m/z ([M+H]+): 251.

2-Mesityl-1*H*-benzo[*d*]imidazole (3e)
Semi-white solid; mp 252-254 °C (lit[25] 253-254 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.42 (s, 1H), 7.65-7.59 (m, 2H), 7.19-7.16 (m, 2H), 7.00 (s, 2H), 2.33 (s, 3H), 2.04 (s, 6H); IR (KBr): 3066, 2822, 2712, 1457, 1321, 723 cm^{-1}. MS (ESI): m/z ([M+H]+): 237.2.

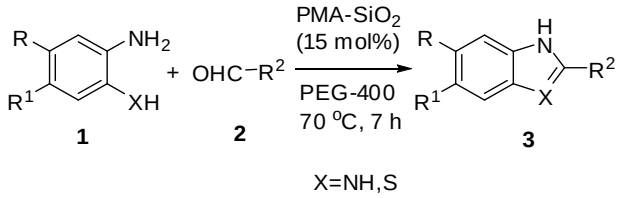
2-(4-Chlorophenyl)-1*H*-benzo[*d*]imidazole (3f)
White solid; mp 295-297 °C (lit[26] 290-292 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.96 (bs, 1H), 8.19 (d, *J* = 8.0 Hz, 2H), 7.66 (q, *J* = 8.0 Hz, 3H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 2H); IR (KBr): 3155, 1656, 1550, 1448, 1429, 1320, 831, 745 cm^{-1}. MS (ESI): m/z ([M+H]+): 229.2.

2-(4-Bromophenyl)-1*H*-benzo[*d*]imidazole (3g)
White solid; mp 286-288 °C (lit[27] 291–294 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.00 (br s, 1H), 8.15-8.18 (m, 2H), 7.80 (d, *J* = 6.80 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.53 (s, 1H), 7.23-7.18 (m, 2H); IR (KBr): 2955, 2733, 1455, 1420, 1299, 1018, 963 cm^{-1}. MS (ESI): m/z ([M+H]+): 274.

2-(Thiophen-2-yl)-1*H*-benzo[*d*]imidazole (3h)
Yellow solid; mp 341-342 °C (lit[26] 341–343 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.95 (brs, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.60-7.54 (m, 2H), 7.20-7.15 (m, 3H); IR (KBr): 3450, 1625, 1572, 1455, 1430, 1280, 1250, 960, 860 cm^{-1}; MS (ESI): m/z ([M+H]+): 201.1.

RESULTS AND DISCUSSION

In preliminary step, the reaction of 1,2-phenylenediamine (**1a,**) and benzaldehyde (**2a**) was carried out at 70 ^{o}C in PEG-400 in presence of PMA-SiO_2 (Scheme 1). The reaction was completed within 7-8 hr with excellent yield 95% without any side product. The recovered catalyst was used for 5 times with effective result.

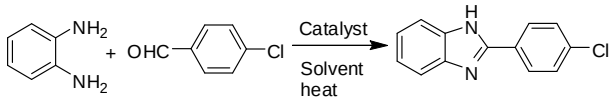


Scheme 1. PMA-SiO_2 catalyzed synthesis of 1,3-benzazoles in PEG-400

To explor the scope of the reaction, the reaction of was carried out by using various catalyst, solvent at different temperatures (Table 1). It was observed that when the reaction was carried out without catalyst at 70 ^{o}C, the product **3a** was isolated in 50% yield (entry 1, Table 1) and the Amberlite was used as catalyst at 70 ^{o}C in PEG-400 for 7 hr

gave **3a** was 60% yield (entry 2, Table 1). Surprisingly, when Amberlite was replaced by PMA-SiO_2 at same temperature, yield was increase upto 95 % (entry 3, Table 1). The use of other acid catalyst such as Amberlite IR 400, and SiO_2, **3a** was also obtained in low yields (entrys 4 and 5, Table 1). The use of other solvents like isopropanol, methanol and acetonitrile was found to be less effective (entrys 6-8, Table 1), when PEG-400 (entrie 3, Table 1) was found to be the most effective solvent.

Table 1. The effect of reaction conditions on condensation of 1a with 2a.[a]



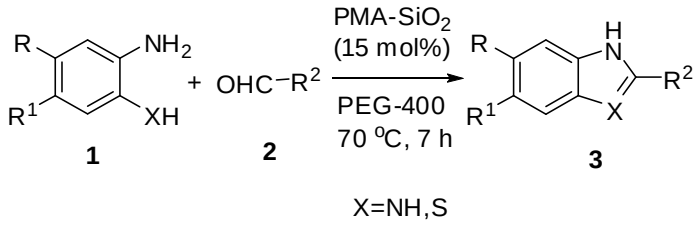
1a **2a** **3a**

Entry	Catalyst	Solvent	T °C; t (h)	Yield (%)[b]
1	No catalyst	PEG-400	70; 7	50
2	Amberlite (15 mol%)	PEG-400	70; 7	60
3	PMA-SiO_2 (15 mol%)	PEG-400	70; 7	92 (92, 90, 89, 87)[c]
4	Amberlite IR 400 (15 mol%)	PEG-400	70; 7	55
5	SiO_2 (15 mol%)	PEG-400	70; 7	65
6	PMA-SiO_2 (15 mol%)	i-PrOH	65; 7	75
7	PMA-SiO_2 (15 mol%)	MeOH	85; 7	85
8	PMA-SiO_2 (15 mol%)	MeCN	85; 7	80
9	PMA-SiO_2 (15 mol%)	PEG-400	65; 7	50
10	PMA-SiO_2 (15 mol%)	PEG-400	80-85; 7	85
11	PMA-SiO_2 (15 mol%)	PEG-400	110-115; 7	80
12	PMA-SiO_2 (5 mol%)	PEG-400	90-95	65
13	PMA-SiO_2 (20 mol%)	PEG-400	90-95	90

[a]*All the reactions were carried out using 1,2-phenylenediamine **1a** (1.0 equiv), aldehyde **2a** in a solvent.*
[b]*Isolated yield.*
[c]*The catalyst was recovered and reused for an additional five runs and the figures within parentheses indicate the corresponding yield for each run.*

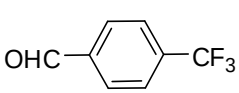
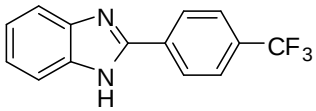
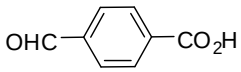
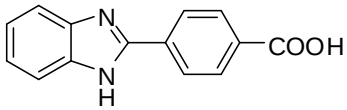
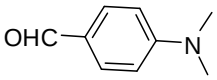
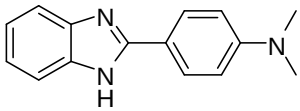
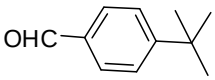
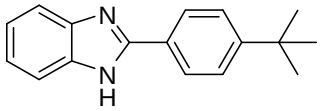
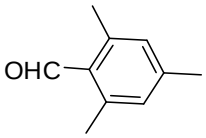
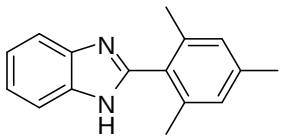
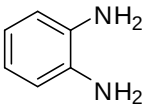
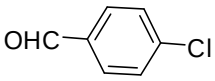
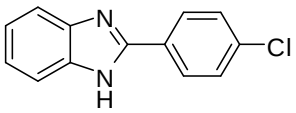
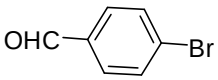
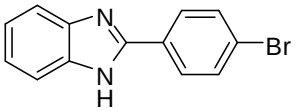
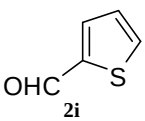
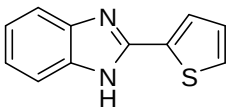
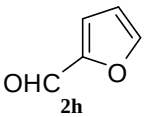
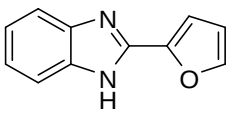
The reaction was also studied under different temperature and amount of catalyst to effect and variation of reaction temperature and the amount of catalyst. The reaction was carried out with different temperatures (entries 9- 11, and 3 Table 1), among them 70 ^oC was found to be the most effective temperature and reaction was completed within 7 hr. To study the effect of catalyst the reaction was carried out with various compositions of PMA-SiO_2 (entries 12 and 13 and 3, Table 1) and the PMA-SiO_2 (15%) (entrie 3, Table 1) was found to be the most effective composition. To test the recyclability of the catalyst used PMA-SiO_2 was recovered by simple filtration and reused in the same reaction and **3a** was isolated without significant loss of its yield. The yield of **3a** was found to be 92, 90, 89 and 87 after 1^{st}, 2^{nd}, 3^{rd} and 4^{th} recovery and reuse of the catalyst. Based on these observations it was evident that a combination of PMA-SiO_2 in PEG-400 was optimal for the preparation of **3a**.

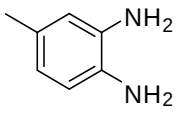
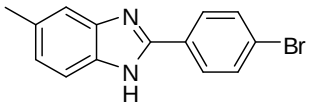
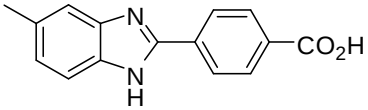
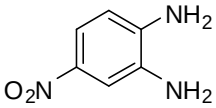
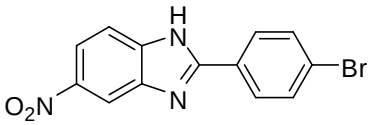
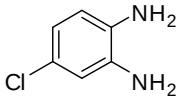
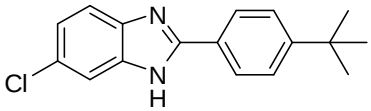
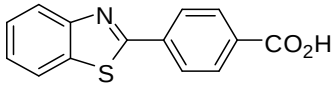
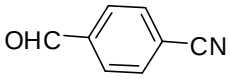
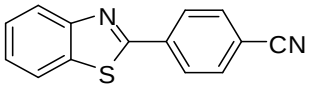
Table 2 PMA/SiO_2 catalysed Synthesis of 2-substituted benzimidazoles and 2-substituted benzothiazoles in PEG-400[a]



1 **2** **3**

X=NH,S

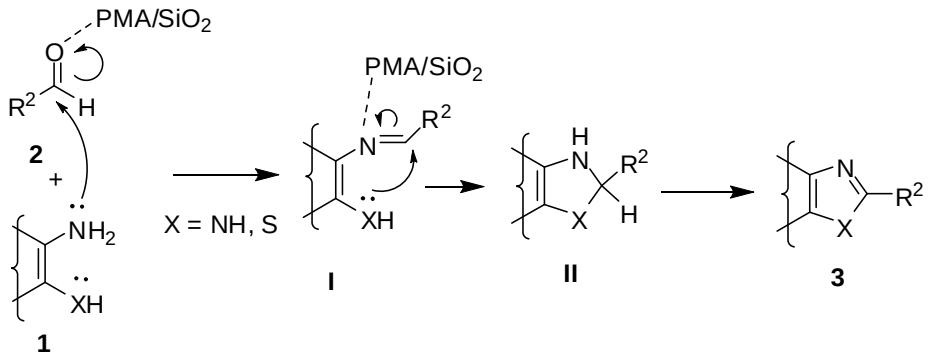
Entry	*o*-phenylenediamines/ *o*-aminobenzenethiol (**1**)	Aldehyde (**2**)	Products (**3**)	Yield (%)[b]
1	**1a**	 **2a**	 **3a**	83
2	**1a**	 **2b**	 **3b**	88
3	**1a**	 **2e**	 **3c**	81
4	**1a**	 **2c**	 **3d**	88
5	**1a**	 **2d**	 **3e**	80
6	 **1a**	 **2a**	 **3f**	85
7	**1a**	 **2b**	 **3g**	86
8	**1a**	 **2i**	 **3h**	90
9	**1a**	 **2h**	 **3i**	89

10	 **1b**	**2b**	 **3j**	84
11	**1b**	**2g**	 **3k**	78
12	 **1d**	**2b**	 **3l**	75
13	 **1c**	**2c**	 **3m**	80
14	**1e**	**2g**	 **3n**	92
15	**1e**	 **2l**	 **3o**	90

[a] *All the reactions were carried out by using o-phenylenediamines or o-aminobenzenethiol **(1)** (1 mmol), aldehyde **(2)** (1 mmol), PMA-SiO_2 (15 mol%) in PEG-400 at 70 °C.*
[c] *Isolated yields.*

To optimize reaction condition for the preparation of benzimidazole compound in hand, we investigated the reaction with various aldehydes. The electron withdrawing groups e.g. CF_3 and COOH (entries 1 and 2, Table 2) or electron donating groups e.g. Cl, Br, and Me (entries 5-7, Table 2), present on the aryl ring of aldehydes were well tolerated. The heteroaromatic (entries 8, 9 Table 2) aldehydes were also successful and afforded to the desired 2-substituted benzimidazoles with high yields.

The scope of this system has been successfully extended to the synthesis of 2-substituted benzothiazole. The reaction was carried out by 2-aminothiophenol instead of 1,2-phenylenediamine, the corresponding 2-aryl benzothiazole derivatives were obtained in excellent yields with various substituents (Table 2, entries 14–15).



Scheme 2. Proposed mechanism for the fomation of 1,3-benzazoles (3)

Mechanistically, the reaction seems to proceed *via* (Scheme 2a) sequence PMA/SiO_2 activated the carbonyl group of aldehydes for imine condensation to form the intermidiate (**I**) and followed by the intramolecular cyclization afforded the intermediate **(II**), Finally, 1,3-hydride transfer afforded 2-disubstituted Benzazoles **3**.

CONCLUSION

In conclusion, we have successfully developed a greener approach for the synthesis of 1,3-Benzazoles (2-substituted benzimidazoles, and 2-substituted benzothiazoles) via a PMA-SiO_2 in PEG-400. The operational simplicity, excellent yields of the products, and high chemoselectivity are the main advantages of this method, and furthermore, this procedure is cost effective , safe and environmentally benign.

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