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INDIAN-860: AN EFFICIENT GREEN SYNTHESIS OF 2-SUBSTITUTED 1,3-BENZAZOLES

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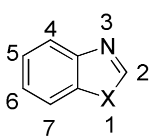
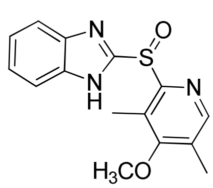
Abstract
An efficient, mild and an eco-friendly method is described to synthesis of 1,3- benzazole by Indian-860 facilitated reaction of 1,2-phenylenediamine / 2-aminothiophenol with alkyl/aryl aldehydes with excellent yield. A range of benzazoles derivatives were prepared by using this green methodology in good yields and Indian-860 was found to be an inexpensive and reusable catalyst.

Keywords: Indian-860, 1,3-benzazoles, PEG-400, green chemistry

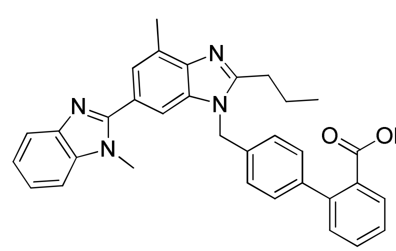
Development of efficient and environmentally friendly synthetic methodologies for the commonly used small organic molecules is one of the major challenges in modern organic synthesis. 1,3-Benzazoles derivatives are very attractive heterocycles in view of its vast application in medicinal chemistry and pharmacology due to their wide range of biological activities [I]. This is exemplified by a range of commonly used drugs such as 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).



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



Omeprazole (**B**)



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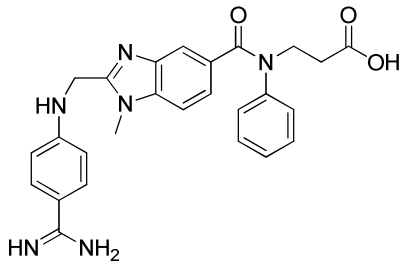
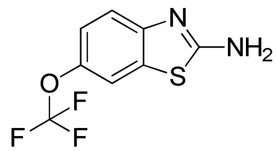
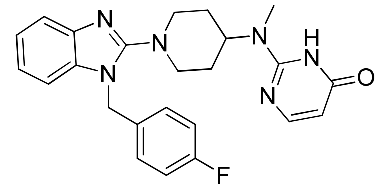


Dabigatran (**D**)



Riluzole (**E**)

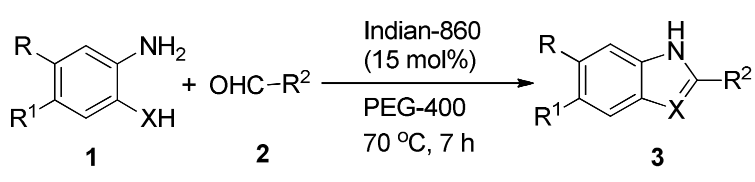


Mizolastin(**F**)

The most generally used synthetic method to access benzimidazole consists in the condensation of carboxylic acids with 1,2-phenylenediamines and their derivatives [II-IV]. The second route involves condensation of aldehydes and 1,2-phenylenediamine followed by oxidative cyclodehydrogenation [V-VI]. Coming to the construction of the 2-substituted benzothiazoles can be synthesized [VII], through (i) condensation–dehydration of 2-aminothiophenol with carboxylic acids [VIII], (ii) condensation with aldehydes under oxidative conditions. [IX] However, many of them though effective, 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.

Indion 860 resin is a commercially available green reagent which can be recovered, activated and reused. It can be easily handled and removed by filtration from the reaction mixture [X, XI]. Thus the process is environmentally benign. To the best of our knowledge, for the synthesis of dihydropyridines, Indion 860 catalysed reaction was not explored. Herein, we wish to describe a new efficient and eco-friendly method to synthesis of dihydropyridines by Indion 860 catalyzed reaction of 1,2-phenylenediamine (**1**), and ethyl-3,3-diethoxypropionate (**2**) (Scheme-1) in presence of PEG-400 with excellent yield.

To the best of our knowledge, for the synthesis of 1,3-benzazole, the Indian-860 catalysed reaction was not explored. Indian-860 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 Indian-860 catalyzed reaction of 1,2-phenylenediamine or 2-aminobenzenethiol (**1**), and aldehyde (**2**) (Scheme-1) in presence of PEG-400 with excellent yield.



Scheme 1**.** Indion 860 catalyzed synthesis of 1,3-benzazole in PEG-400

1. Experimental

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 tetra methylsilane (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), aldehyde (**2**) (1 mmol) and Indian-860 (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 mixture was diluted with Et_2O. The catalyst, i.e. Indian-860 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.

6-phenyl-5H-[1,3]dioxolo[4',5':4,5]benzo[1,2-d]imidazole (3a)

White solid; mp 221-225 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.72 (bs, 1H), 7.71-7.67 (m, 2H), 7.53-7.50 (m, 2H), 7.18-7.14 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.18 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 153.2, 141.5 (2C), 135.1, 131.0 (2C), 129.8 (2C), 128.2, 128.0 (2C), 102.2 (2C), 99.9; IR (KBr): 3435, 1345, 1232, 1133 cm^{-1}; m/z ([M+H]+): 239.1.

2-(4-(Benzyloxy)phenyl)-1*H*-benzo[d]imidazole (3b)

White solid, mp 255-258 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.72 (bs, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.59-7.48 (m, 4H), 7.24-7.16 (m, 7H), 5.16 (s, 2H), 7.24-7.21 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 158.2, 152.7, 142.1 (2C), 136.3, 129.9 (2C), 129.6 (2C), 126.6(2C), 127.6, 123.0 (2C), 116 (2C), 115.3(2C), 114.5, 68.8; IR (KBr): 3061, 2920, 1700, 1380, 1290, 1110 cm^{-1}; MS (ESI): m/z ([M+H]+): 301.1

4-(1*H*-Benzo[*d*]imidazol-2-yl)-*N*,*N*-dimethylaniline (3c)

Yellow solid; mp 284-285 °C (lit[XII] 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}; MS (ESI): m/z ([M+H]+): 238.2.

2-(4-(Tert-butyl)phenyl)-1*H*-benzo[*d*]imidazole (3d)

White solid; mp 252-253 °C (lit[XIII] 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 253-254 °C (lit[XIV] 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 296-297 °C (lit[XV] 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 286-287 °C (lit[5b] 291–294 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ

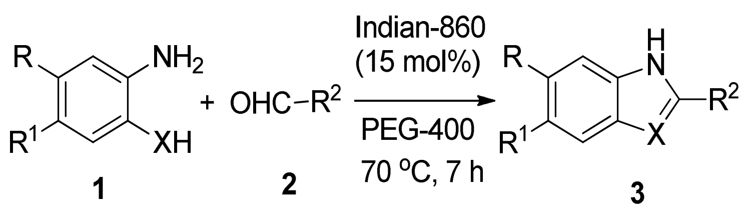
13.00 (br s, 1H), 8.15-8.18 (m, 2H), 7.80 (d, J = 6.80 Hz, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.53 (s, 1H), 7.23-7.18 (m, 2H); IR (KBr): 2955, 2733, 1455, 1420, 1299, 1018, 963 cm^{-1}. MS (ESI): m/z ([M+H]+): 274.

2-(Thiophen-2-yl)-1*H*-benzo[*d*]imidazole (3h)

Yellow solid; mp 342-343 °C (lit[XV] 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.

2. Results and discussion

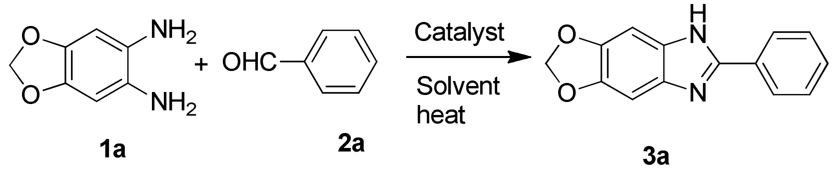
At first the reactions with 1,2-phenylenediamine (**1a**) and aldehyde (**2a**) were carried out using various catalyst, solvent and temperatures and the results are summarized in Table 1. When the reaction was carried in the presence of $FeCl_3$ at 70°C, the product **3a** was isolated in 25% yield (entry 1, Table 1). When the Indian-860 was used as catalyst at 70°C in PEG-400 for 6 hr gave **3a** was 50% yield (entry 2, Table 1). Surprisingly, when *p*-TSA was replaced by Indion-860, it provides 95 % yield (entry 3, Table 1). The use of other catalyst such as Amberlite and *p*-TSA were used, **3a** was obtained in low yields (entry 4 and 5, Table 1). The use of water as solvent was found to be less effective (entry 6, Table 1), when PEG-400 (entry 3, Table 1) was found to be the most effective solvent. The reaction was then carried out with different temperatures (entry 7 and 8, Table 1), 70°C was found to be the most effective temperature and reaction will complete within 7 hr. To test the recyclability of the catalyst used Indion 860 was recovered by simple filtration and reused in the same reaction when **3a** was isolated without significant loss of its yield. The yield of **3a** was found to be 90, 88, 86 and 84 after 1st, 2nd, 3rd and 4th recovery and reuse of the catalyst. Based on these observations it was evident that a combination of Indion 860 in PEG-400 was optimal for the preparation of **3a**.



X=NH,S

Scheme 1. Indian-860 catalyzed synthesis of 1,3-benzazoles in PEG-400

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

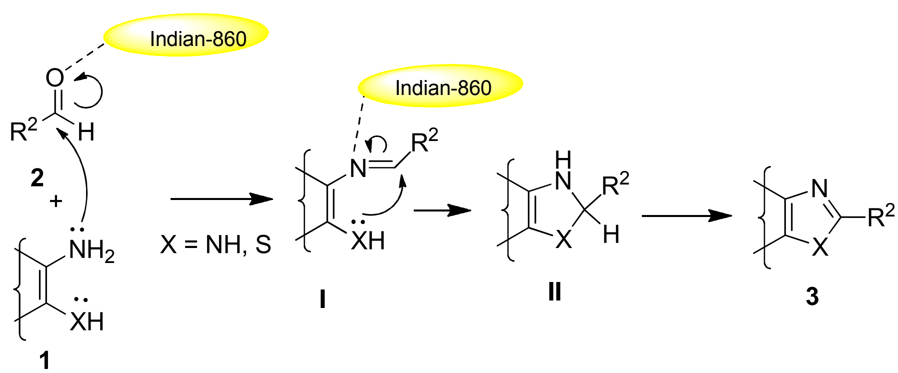


S. No	Catalyst	Solvent	T °C	Yield (%)[b]
1	$FeCl_3$ (2.5 mol%)	PEG-400	70	25
2	SiO_2 (20 mol%)	PEG-400	70	50

3	Indion 860 (20 mol%)	PEG-400	70	95 (92, 88, 86, 84)[c]
4	Amberlite (20 mol%)	PEG-400	70	35
5	*p*-TSA (2.5 mol%)	PEG-400	70	trace
6	Indion 860 (20 mol%)	Water	65	30
7	Indion860 (20 mol%)	PEG-400	50	35
8	Indion 860 (20 mol%)	PEG-400	115	75

[a]All the reactions were carried out using 1,2-phenylenediamine **1a** (1.0 equiv), aldehyde **2a** in a solvent for 7 h.
[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.

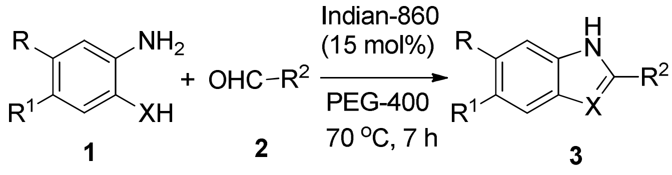
To optimize reaction condition for the preparation of benzimidazole compound in hand, we investigated the reaction with various aldehydes. The electron withdrawing groups e.g. COOH (entries 10 and 14, Table 2) or electron donating groups e.g. Cl, Br, and Me (entries 5-7, Table 2), present on the aryl ring of aldehydes were well tolerated. The hetero aromatic (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 substituent's (Table 2, entries 14–15).



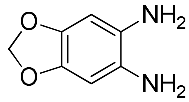
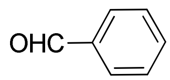
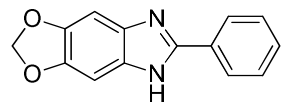
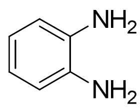
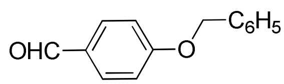
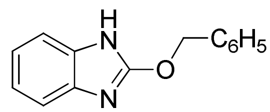
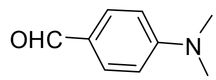
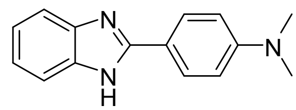
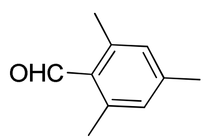
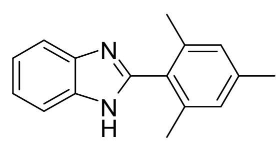
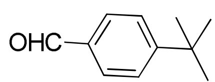
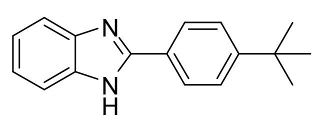
Scheme 2. Proposed mechanism for the fomation of 1,3-benzazoles (**3**)

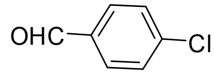
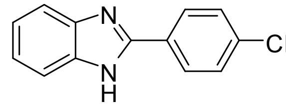
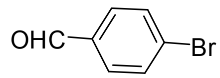
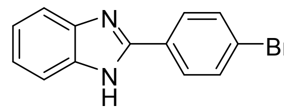
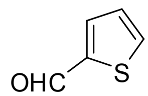
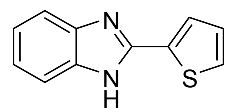
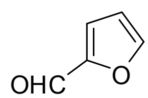
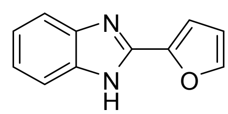
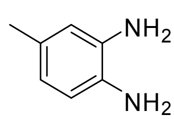
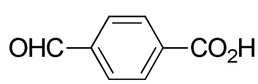
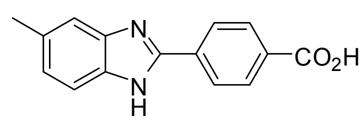
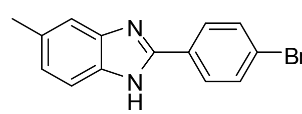
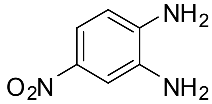
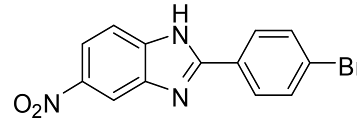
Mechanistically, the reaction seems to proceed *via* (Scheme 2a) sequence Indian-860 activated the carbonyl group of aldehydes for imine condensation to form the intermediate (**I**) and followed by the intramolecular cyclization afforded the intermediate **(II**), Finally, 1,3-hydride transfer afforded 2-disubstituted Benzazoles **3**.

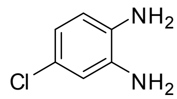
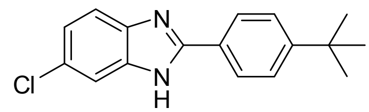
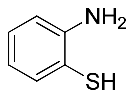
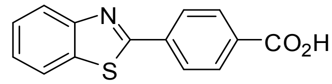
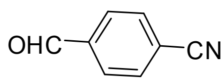
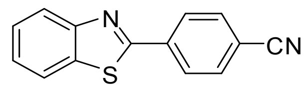
Table 2 : Indian-860 catalyzed Synthesis of 2-substituted benzimidazoles and 2-substituted benzothiazoles in PEG-400[a]



X=NH,S

Entry	*o*-phenylenediamines/ *o*-aminobenzenethiol (**1**)	Aldehyde (**2**)	Products (**3**)	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	95
2	 **1b**	 **2b**	 **3b**	89
3	**1b**	 **2c**	 **3c**	85
4	**1b**	 **2d**	 **3d**	85
5	**1b**	 **2e**	 **3e**	85

6	**1b**	 **2f**	 **3f**	88
7	**1b**	 **2g**	 **3g**	88
8	**1b**	 **2h**	 **3h**	92
9	**1b**	 **2i**	 **3i**	92
10	 **1c**	 **2j**	 **3j**	88
11	**1c**	**2g**	 **3k**	85
12	 **1d**	**2g**	 **3l**	82

13	 **1e**	**2e**	 **3m**	85
14	 **1f**	**2j**	 **3n**	90
15	**1f**	 **2k**	 **3o**	92

[a]All the reactions were carried out by using *o*-phenylenediamines or *o*-aminobenzenethiol (**1**) (1 mmol), aldehyde (**2)** (1 mmol), Indian-860 (15 mol%) in PEG-400 at 70 °C.
[c]Isolated yields.

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 Indian-860 in PEG-400. The operational simplicity, excellent yields of the products, and high chemo selectivity are the main advantages of this method, and furthermore, this procedure is cost effective, safe and environmentally benign.

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