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Nano indium oxide: an efficient catalyst for the synthesis of 1,2-disubstituted benzimidazoles in aqueous media

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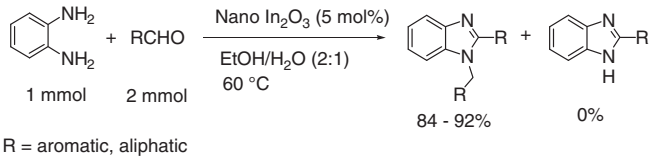
ABSTRACT

Synthesis of 1,2-disubstituted benzimidazoles has been developed by the condensation of diamine with aldehydes using nano In_2O_3 as an efficient catalyst under mild reaction conditions in aqueous media. The procedure is applicable to aryl, aliphatic, heteroaryl aldehydes. In_2O_3 nanoparticles are recyclable without the loss of significant catalytic activity.

Benzimidazole and its derivatives are very important compounds due to their pharmacological[1] and biological activities.[2] Many commercial medicines such as Liarozole,[3] Omeprazole,[4] Thiabendazole[5], and Domperidone[6] contain benzimidazole and its analogue dihydrobenzimidazole. A few methods are available for the synthesis of 1,2-disubstituted benzimidazoles like N-alkylation of *o*-nitroanilides followed by reductive cyclization,[7] N-alkylation of 2-substituted benzimidazole in the presence of a strong base,[8] cyclocondensation of N-substituted *o*-aminoanilides,[9] and the condensation of N-substituted phenylenediamines with the sodium salt of α-hydroxybenzylsulfonic acid.[10] Another protocol is the direct condensation of 1,2-phenylenediamines with aryl aldehydes using a variety of catalysts such as acetic acid,[11] SDS micelles,[12] cobalt(II) chloride,[13] trimethylsilyl chloride,[14] Amberlite IR-120[15] and organocatalyst like L-proline.[16] But very few methods are less selective in terms of *N*-1 substitution, as a result 2-substituted benzimidazole along with 1,2-disubstituted benzimidazole is formed. All these methodologies are applicable to aryl aldehydes only. To the best of our knowledge there is only one example for acyclic aldehyde reported by Radatz et al.[17] Metal nanoparticles have attracted considerable interest in synthetic organic chemistry due to their high catalytic activity, reusability and benign character in the context of green chemistry.[18] However, nano In_2O_3 catalyzed reactions are rare in organic synthesis.[18i,19a] In continuation of our research work using nano In_2O_3 and indium[19] in organic synthesis here we are pleased to report that a mixture of aldehyde, phenylenediamine in the presence of nano In_2O_3 (5 mol %) in an EtOH/H_2O (2:1) mixture at 60 °C furnished 1,2-disubstituted benzimidazoles in good yields (Scheme 1).

The experimental procedure[20] is very simple, a mixture of aldehyde (2 mmol), phenylenediamine (1 mmol) was stirred in the presence of nano In_2O_3 (5 mol %) in an EtOH/H_2O (2:1) mixture at 60 °C for a certain period as required for the completion (TLC). To optimize the reaction conditions we have used nano In_2O_3 for the direct condensation between phenylenediamine (1 mmol) and benzaldehyde (2 mmol) under different concentrations and using different solvents as summarized in Table 1. Nano In_2O_3 (5 mol %) was better suited to afford 1,2-disubstituted benzimidazoles in an ethanol/water (2:1) mixture at 60 °C. Ethanol/water (2:1) mixture appeared to be the best choice among the common solvents such as MeOH, CH_3CN, THF, toluene, dioxane. Lower conversions were obtained when indium oxide powder and other metal catalysts such as NiO (nano), CuO (nano), and ZnO (nano) were used. Negligible amount of the product was formed in the absence of catalyst.



Scheme 1. Synthesis of 1,2-disubstituted benzimidazoles.

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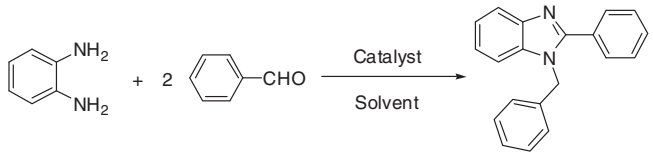
Table 1
Optimization of reaction conditions[a]



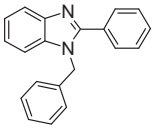
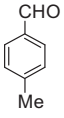
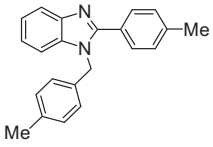
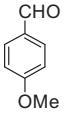
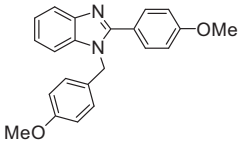
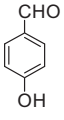
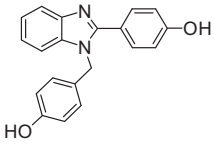
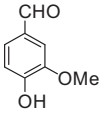
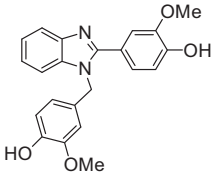
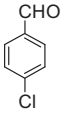
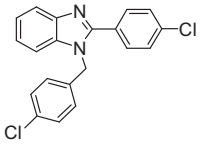
Entry	Catalyst	Solvents	Time (h)	Yield[b] (%)
1	—	EtOH/H_2O (2:1)	5	<25
2	NiO (nano, 5 mol %)	EtOH/H_2O (2:1)	5	46
3	CuO (nano, 5 mol %)	EtOH/H_2O (2:1)	5	42
4	ZnO (nano, 5 mol %)	EtOH/H_2O (2:1)	5	45
5	In_2O_3 (powder, 5 mol %)	EtOH/H_2O (2:1)	5	67
6	In_2O_3 (nano, 5 mol %)	EtOH	2	76
7	In_2O_3 (nano, 5 mol %)	H_2O	2	63
8	In_2O_3 (nano, 5 mol %)	EtOH/H_2O (2:1)	2	89
9	In_2O_3 (nano, 2 mol %)	EtOH/H_2O (2:1)	5	62
10	In_2O_3 (nano, 10 mol %)	EtOH/H_2O (2:1)	2	90
11	In_2O_3 (nano, 5 mol %)	EtOH/H_2O (2:1)	2	76
12	In_2O_3 (nano, 5 mol %)	EtOH/H_2O (2:1)	2	78
13	In_2O_3 (nano, 5 mol %)	MeOH	5	72
14	In_2O_3 (nano, 5 mol %)	MeOH/H_2O (2:1)	5	81
15	In_2O_3 (nano, 5 mol %)	MeOH/H_2O (1:1)	5	74
16	In_2O_3 (nano, 5 mol %)	MeCN	5	43
17	In_2O_3 (nano, 5 mol %)	THF	5	46
18	In_2O_3 (nano, 5 mol %)	Toluene	5	57
19	In_2O_3 (nano, 5 mol %)	Dioxane	5	52

[a] Stirring at 60 °C.
[b] Isolated yield.

A wide range of aliphatic, aromatic, heteroaryl, and α,β-unsaturated aldehydes were subjected to prove the general applicability of our present procedure which is summarized in Table 2. Several sensitive functionalities such as –OH, OMe, halogen (Cl, Br) are unaffected under the present reaction conditions. Heteroaryl aldehydes such as pyridine-2-carboxaldehye and furfural also afforded desired products in good yields. α,β-Unsaturated aldehyde such as cinnamaldehyde reacted well under these conditions. In general, the reactions are fast, and clean. No detectable side products have been traced. 1,2-Disubstituted benzimidazole derivatives were formed in all the cases. However, the synthesis of unsymmetrical 1,2-disubstituted benzimidazole was unsuccessful under the present reaction conditions. Recyclability of In_2O_3 nanoparticles was also studied and the catalyst is recyclable without the loss of significant catalytic activity. In a typical experiment the catalyst was reused for three times (recovery amount, 90% and yield, 82% after 3rd run for entry 1, Table 2).

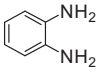
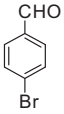
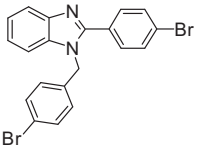
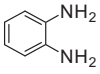
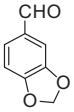
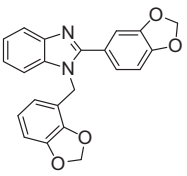
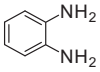
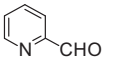
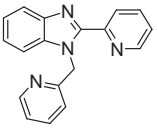
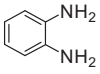
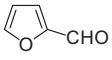
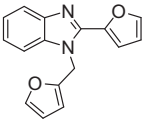
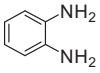
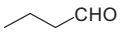
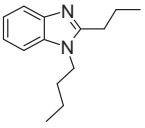
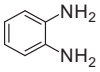
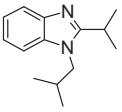
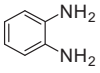
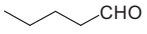
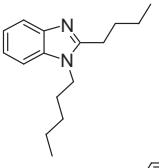
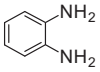
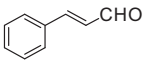
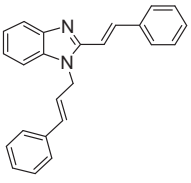
In conclusion, nano In_2O_3 has been found to be an efficient catalyst for the synthesis of 1,2-disubstituted benzimidazoles by the condensation of diamine with aldehyde in aqueous media. General applicability, operational simplicity, mild reaction conditions, and aqueous reaction media are the notable advantages of the present procedure. We believe that our new protocol using nano In_2O_3 will find widespread applications in academic laboratories and industry.

Table 2
Synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazole

Entry	Diamine	Aldehydes	Products	Time (h)	Yield[a] (%)
1				2	89
2				2	91
3				2.5	88
4				3.75	87
5				4	89
6				3.5	85

(*continued on next page*)

Table 2 (*continued*)

Entry	Diamine	Aldehydes	Products	Time (h)	Yield[a] (%)
7				3	86
8				2.5	92
9				2.5	84
10				3	82
11				2.5	86
12				2.5	87
13				2.75	83
14				2.5	84

[a] Isolated yield.

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20. Typical procedure for the synthesis of 2-benzo[1,3]dioxol-5-yl-1-benzo[1,3]dioxol-4-yl-methyl-1*H*-benzoimidazole (Table 2, entry 8): A mixture of *o*-phenylenediamine (107 mg, 1 mmol) and piperonal (300 mg, 2 mmol) was stirred in the presence of commercially available nano In_2O_3 (5 mol %) in an EtOH/H_2O (2:1) mixture (5 ml) at 60 °C for 2 h (TLC). After completion, the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL) and nano In_2O_3 was recovered by centrifugation. The reaction mixture was extracted with diethyl ether (2 × 10 mL) and dried over Na_2SO_4. Evaporation of solvent furnished the crude product which was recrystallized from methanol to afford the analytically pure product as a yellow solid (342 mg, 92%). Yellow solid. Mp 143–144 °C. IR (KBr) 3434, 2906, 1454, 1247 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, J = 8 Hz, 1H), 7.30–7.15 (m, 5H), 6.87 (d, J = 8 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H), 6.56–6.55 (m, 2H), 6.02 (s, 2H), 5.93 (s, 2H), 5.34 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9, 149.2, 148.5, 148.1, 147.4, 143.1, 136.1, 130.3, 123.9, 123.7, 123.1, 122.8, 119.9, 119.4, 110.5, 109.8, 108.8, 108.7, 106.7, 101.6, 101.4, 48.3. Anal. Calcd for $C_{22}H_{16}N_2O_4$: C, 70.96; H, 4.33; N, 7.52. Found: C, 70.82; H, 4.26; N, 7.43. 1-Butyl-2-propyl-1*H*-benzoimidazole (Table 2, entry 11): Brown liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75–7.73 (m, 1H), 7.31–7.29 (m, 1H), 7.25–7.22 (m, 2H), 4.10 (t, J = 7.6 Hz, 2H), 2.86 (t, J = 7.8 Hz, 2H), 1.96–1.80 (m, 2H), 1.82–1.74 (m, 2H), 1.43–1.37 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 141.9, 134.8, 122.1, 121.9, 118.9, 109.4, 43.5, 31.9, 29.2, 21.2, 20.2, 14.1, 13.7. Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.64; H, 9.23; N, 12.84. 1-Isobutyl-2-isopropyl-1*H*-benzoimidazole (Table 2, entry 12): Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.78–7.76 (m, 1H), 7.30–7.26 (m, 1H), 7.23–7.20 (m, 2H), 3.92 (d, J = 8 Hz, 2H), 3.22–3.16 (m, 1H), 2.26–2.15 (m, 1H), 1.44 (d, J = 8 Hz, 6H), 0.95 (d, J = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 141.9, 134.7, 121.7, 121.5, 118.7, 109.6, 50.5, 34.0, 29.0, 26.0, 21.6, 19.9, 19.0. Anal. Calcd. for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.67; H, 9.21; N, 12.82. 2-Butyl-1-pentyl-1*H*-benzoimidazole (Table 2, entry 13): Yellow liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.74–7.72 (m, 1H), 7.30–7.27 (m, 1H), 7.24–7.20 (m, 2H), 4.08 (t, J = 7.4 Hz, 2H), 2.86 (t, J = 7.8 Hz, 2H), 1.89–1.78 (m, 4H), 1.50–1.33 (m, 6H), 1.00–0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 142.4, 134.9, 122.0, 121.8, 119.5, 109.3, 43.7, 30.0, 29.6, 29.1, 27.1, 22.7, 22.4, 13.9 (2C). Anal. Calcd for $C_{16}H_{24}N_2$: C, 78.64; H, 9.90; N, 11.46. Found: C, 78.51; H, 9.78; N, 11.35. 1-(3-Phenyl-allyl)-2-styryl-1*H*-benzoimidazole (Table 2, entry 14): Brown oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 16 Hz, 1H), 7.85 (d, J = 8 Hz, 1H), 7.60–7.03 (m, 14H), 6.44 (d, J = 15.5 Hz, 1H), 6.36–6.30 (m, 1H), 5.04 (d, J = 4.5 Hz, 1H), 4.99 (d, J = 4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.8, 142.3, 138.8, 135.9, 135.8, 135.1, 134.6, 132.8, 130.4, 129.4, 129.1, 129, 128.8, 128.3 (2C), 127.6, 126.7, 123.3, 123.2, 123.1, 119.2, 112.4, 109.8, 45.5. Anal. Calcd for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.54; H, 5.89; N, 8.24.