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PEG-mediated catalyst-free expeditious synthesis of 2-substituted benzimidazoles and bis-benzimidazoles under solvent-less conditions

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ABSTRACT

A wide variety of 2-substituted benzimidazoles and bis-benzimidazoles were synthesized in high yields by PEG-mediated catalyst-free synthesis under solvent-less conditions. The products were directly recrystallized from hot methanol. The reaction occurred giving excellent yields with low as well as high molecular weight PEGs.

1. Introduction

Over the past few decades, environmentally benign chemical processes have gained considerable interest both in the academia and in industry.[1] Volatile, toxic and hazardous organic solvents are continuously being replaced either by the use of solvent-free techniques,[2] or by using ionic liquids,[3] water[4a] or phase-transfer catalysts.[4b] The application of PEG as a reaction medium is highly beneficial as the system remains neutral, which helps in maintaining a wide variety of functional groups unchanged that are either acid or base susceptible.

2. Results and discussion

In continuation of our efforts in searching for newer synthetic methodologies for biologically important heterocycles,[5,6,7a,b] we chose 2-substituted benzimidazoles as targets. Benzimidazoles are present in various bioactive compounds possessing antiviral, antihypertension and anticancer properties.[8,9] Compounds possessing the benzimidazole moiety express significant activity against several viruses such as HIV,[10] Herpes (HSV-1),[11] human cytomegalovirus (HCMV)[10] and influenza.[12] Bis-benzimidazoles are DNA-minor grove binding agents possessing anti-tumour activity.[13]

Since organic synthesis in PEG under solvent-less conditions is an area of very high significance in modern organic synthesis,[4b,14,15] we examined the synthesis of benzimidazoles in PEG 400. PEG is inexpensive, non-toxic, possesses high thermal stability, is recyclable and helps in maintaining a neutral reaction medium.

In order to standardize the reaction, 4-chlorobenzaldehyde (4 mmol) and 1,2-phenylenediamine (4.5 mmol) were heated in an oil-bath at 110 °C for 4 h without any catalyst but with PEG 400 (0.1 mL) (Scheme 1, Table 1). On cooling to room temperature (25 °C), the reaction mixture solidified, and the final product was recrystallized directly from hot methanol without any need for further purification. The results of the study of this standard reaction for its optimization are summarized in Table 1. We find that the reaction proceeded best under solvent-less conditions rather than using solvents. The best result was obtained with 0.1 mL of PEG 400 for 4 mmol of 4-chlorobenzaldehyde under solvent-free conditions (Table 1, entry 4). Using more than 0.1 mL of PEG 400 did not improve the yield of the product, and at the same time, no reaction took place in the absence of PEG 400. Thus, the use of PEG is absolutely essential in this reaction. Since only 0.1 mL of PEG 400 is used it cannot act as a solvent, thus it is the promoter for the reaction without requiring any additional acid catalyst. No formation of benzimidazole took place under argon atmosphere (the reaction stopping at the imine stage) indicating that the aerial oxygen is absolutely necessary for the oxidation step. We investigated our protocol with various PEGs with molecular weights 200, 400, 4000, 6000 and 9000 (0.01 mol % each) for our model reaction with

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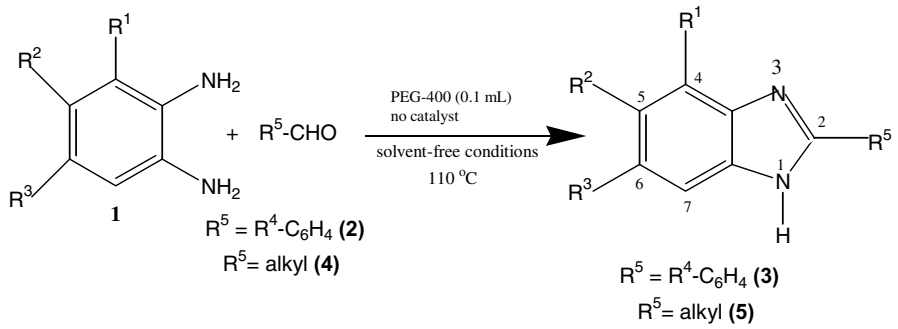


(For various R^1, R^2, R^3, R^4 and R^5 refer to Tables 2A and 2B)

Scheme 1.

Table 1
Synthesis of 2-(4′-chlorophenyl)-benzimidazole under various conditions (entry 4 gives the optimum conditions)

Entry	PEG 400 (mL)	Solvent (mL)	Reaction medium temperature	Time (hours)	Yield (%) (isolated)
1	—	—	110 °C	20	—
2	0.05	—	99 °C	20	35
3	0.05	—	110 °C	15	50
4	0.1	—	110 °C	4	95
5	0.2	—	110 °C	4	90
6	0.4	—	110 °C	4	80
7	0.1	—	99 °C	20	35
8	0.1	EtOH (5)	Reflux	20	30
9	0.1	DMF (5)	Reflux	20	42
10	0.1	THF (5)	Reflux	20	38
11	0.1	CH_3CN (5)	Reflux	20	40
12	—	Any above solvent (5)	Reflux	50–55	—
13	0.1	—	Microwave oven 110 °C, 600 W	1	70

4-chlorobenzaldehyde (4 mmol) and 1,2-phenylenediamine (4.5 mmol). The reaction occurred giving excellent yields of the product (95–88%) with low as well as high molecular weight PEGs.

With the above result in hand, a variety of aldehydes, aliphatic **4**, heterocyclic and aromatic **2**, possessing both electron-donating and electron-withdrawing groups were employed for benzimidazole formation and in all the cases, the yields were excellent (Scheme 1, Table 2A and B). Five different *ortho*-phenylenediamines **1** were employed and all of them reacted smoothly under the reaction conditions. All the known products were characterized by comparing their physical and spectral (IR, ^{1}H NMR and ^{13}C NMR) data with those of the authentic samples reported in the literature. The data for the selected previously unknown compounds (Table 2A, entries 19, 21 and 32 and Table 3, entry 6) are reported in this Letter. The data for all other previously unknown compounds are given in the Supplementary data.

The mechanism of the benzimidazole formation is well documented.[26] The initial formation is of the imine normally with trans stereochemistry.[26] The imine **6** obtained from the reaction of 4,5-dichloro-1,2-phenylenediamine and 4-cyanobenzaldehyde was isolated, purified and characterized. The imine then cyclizes, followed by oxidation and dehydration to form the final product (Table 2A, entry 32).

Encouraged by the above results, we turned our attention to the synthesis of the bis-benzimidazoles starting from benzene dialdehydes. For this purpose, two benzene dialdehydes 1, 4 (**7**) and 1, 3 (**9**) were chosen, and applying our methodology at 140 °C in an oil-bath, the bis-benzimidazoles were synthesized (Scheme 2) in excellent yields, as summarized in Table 3.

Table 2A
Synthesis of 2-aryl-substituted benzimidazoles with PEG 400 (0.1 mL) under solventless conditions in an oil-bath at 110 °C

Entry	Product **3** (from **2**)				Time (hours)	Yield[a] (%)	References
	R^1	R^2	R^3	R^4			
1	H	H	H	H	6	90	16
2	H	H	H	4-OH	7	92	17
3	H	H	H	2-OMe	5	92	18
4	H	H	H	4-CN	8	90	19
5	H	H	H	4-Cl	4	95	16
6	H	H	H	3-OH	9	87	20
7	Me	H	H	H	6	89	21
8	Me	H	H	4-CN	8	93	22
9	Me	H	H	2-OH	7	92	23
10	H	Me	H	3-OMe-4-OH	7	94	24
11	H	Me	H	4-OH	8	88	24
12	H	Me	H	3,4-$(OMe)_2$	5	86	24
13	H	Me	H	2-OMe	6	88	25
14	H	Me	H	3-NO_2	4	91	26
15	H	Me	H	4-NMe_2	6	90	24
16	H	Me	H	2-Cl	8	93	26
17	H	Me	H	2-OH	8	92	26
18	H	Me	H	4-CN	9	95	25
19	H	Me	H	2,5-$(OMe)_2$	4	89	—
20	H	Me	Me	4-CN	9	86	27
21	H	Me	Me	2-OMe	7	87	—
22	H	Me	Me	2-OH	7	91	28
23	H	Me	Me	R_4-C_6H_4=2-furanyl	8	93	29
24	H	Me	Me	4-Cl	4	92	—
25	H	Me	Me	4-Br	3	87	—
26	H	Me	Me	2,5-$(OMe)_2$	5	88	—
27	H	Me	Me	3-Br	2	87	—
28	H	Me	Me	3,4-$(OMe)_2$	5	89	—
29	H	Me	Me	3-NO_2	4	90	—
30	H	Cl	Cl	4-Cl	4	87	—
31	H	Cl	Cl	2,5-$(OMe)_2$	5	83	—
32	H	Cl	Cl	4-CN	9	82	—
33	H	Cl	Cl	3,4-$(OMe)_2$	7	85	—
34	H	Cl	Cl	3-OMe-4-OH	8	87	—
35	H	Cl	Cl	R_4-C_6H_4=2-furanyl	6	93	—

[a] Isolated yields.

On directly comparing our methodology with some very recent solvent-free techniques for the benzimidazole formation[25,36–39] (i) this methodology succeeded with a variety of substrates (17 new compounds were synthesized), (ii) synthesis of benzimidazoles from 4,5-dichloro-*ortho*-phenylenediamine produced a number of previously unknown benzimidazoles (Table 2A, entries 30–35), (iii) a catalyst is not required and (iv) the methodology is readily applicable to the synthesis of bis-benzimidazoles.

Table 2B
Synthesis of 2-alkyl-substituted benzimidazoles with PEG 400 (0.1 mL) under solvent-less conditions in an oil-bath at 110 °C

Entry	Product **5** (from **4**)				Time (hours)	Yield[a] (%) (isolated)	References
	R^1	R^2	R^3	R^5			
1	H	H	H	$-CH_3$	5	75	30
2	H	Me	Me	$-CH_3$	6	79	31
3	H	Cl	Cl	$-CH_2CH_3$	6	77	32
4	H	Cl	Cl	$-CH_2CH_2CH_3$	6	74	33

[a] Isolated yields.

Table 3
Synthesis of bis-benzimidazoles with PEG 400 (0.1 mL) in an oil-bath at 140 °C

Entry	Starting aldehyde (Scheme 2)	Product (**8** from **7**, **10** from **9**)			Time (hours)	Yield[a] (%)	References
		R^1	R^2	R^3			
1	**7**	H	H	H	7	85	26
2	**7**	H	Me	H	8	87	26
3	**9**	H	H	H	8	83	34
4	**9**	H	Me	Me	9	80	—
5	**9**	H	Me	H	6	86	35
6	**9**	H	Cl	Cl	8	68	—

[a] Isolated yields.

3. General experimental procedure for 2-substituted benzimidazole formation

A mixture of an aldehyde (4 mmol), substituted *ortho*-phenylenediamine (4.5 mmol) and PEG 400 (0.1 mL) were taken in a dry round-bottomed flask (50 mL). The flask was placed in an oil-bath at a temperature of 110 °C fitted with a condenser. The reaction mixture was heated for the specified time (Tables 2A and B). The reaction was monitored by TLC till the disappearance of the starting aldehyde. On cooling to room temperature (25 °C), the reaction mixture solidified, and product was directly recrystallized from hot methanol to afford the pure benzimidazoles. The mother liquor was concentrated further to obtain some more product, and thus the total yield was calculated. For a 50 mmol-scale reaction with 4-chlorobenzaldehyde and 1,2-phenylenediamine, the mother liquor after two precipitations was concentrated under vacuum to obtain the PEG 400, which was washed with water, dried and used further. In this manner, PEG 400 could be recycled up to 6 cycles.

[For the synthesis of the bis-benzimidazoles, the dialdehyde (4 mmol) was mixed with substituted 1,2-phenylenediamines (9 mmol) and heated at 140 °C using the same methodology for the benzimidazoles for the time period as mentioned in Table 3].

All the known compounds were characterized by comparing their physical and spectral data with those of reported compounds. The mps, IR, ^{1}H NMR and ^{13}C NMR data of the isolated imine **6** and the unknown benzimidazoles (Table 2A, entries 19, 21 and 32) and one bis-benzimidazole (Table 3, entry 6) are given below:

3.1. 1-(4′-Cyanophenyliminyl)-4,5-dichloroaniline (6)

Mp 300–302 °C (EtOAc). IR (KBr): 3466, 3370, 2926, 2373, 2222, 1610, 1477, 1267, 1129, 957 and 831 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.53 (s, 1H, –CH=N), 8.00 (d, J = 8.4 Hz, 2H, $C_{3'}$–H and $C_{5'}$–H), 7.76 (d, J = 8.4 Hz, 2H, $C_{2'}$–H and $C_{6'}$–H), 7.24 (s, 1H, C_6–H), 6.87 (s, 1H, C_3–H), 4.36 (br s, 2H, $-NH_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.71 (–CH=N), 142.39 (C_1), 139.57 (C_2), 134.92 (C_4 and C_5), 132.59 ($C_{3'}$ and $C_{5'}$), 131.97 ($C_{1'}$), 129.06 ($C_{2'}$ and $C_{6'}$), 120.96 (CN), 118.33 (C_6), 116.37 (C_3), 114.62 ($C_{4'}$). Anal. Calcd for $C_{14}H_9N_3Cl_2$; C: 57.95, H: 3.13, N: 14.48%. Found: C: 58.09, H: 3.03, N: 14.56%.

3.2. 2-(2′,5′-Dimethoxyphenyl)-5-methyl-1*H*-benzimidazole (Table 2A, entry 19)

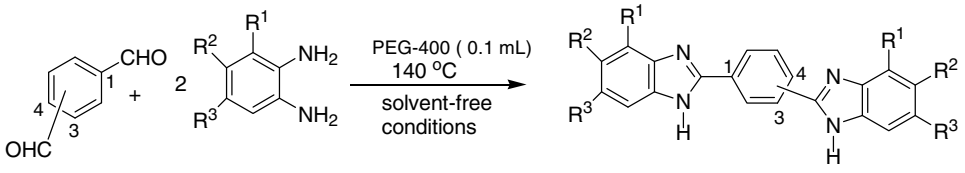
Mp 170–172 °C (EtOAc). IR (KBr): 3227, 2932, 1612, 1489, 1433, 1212, 1041, 807 and 736 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.67 (br s, 1H, –NH), 8.10 (d, J = 1.5 Hz, 1H, $C_{6'}$–H), 7.78–7.55 (br d, 1H, C_7–H), 7.43–7.28 (br d, 1H, C_4–H), 7.09 (d, J = 8.1 Hz, 1H, C_6–H), 7.02–6.90 (m, 2H, $C_{3'}$–H and $C_{4'}$–H), 4.01 (s, 3H, $C_{2'}$–OCH_3), 3.88 (s, 3H, $C_{5'}$–OCH_3), 2.49 (s, 3H, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.22 ($C_{2'}$ and $C_{5'}$), 151.12 (C_2), 149.70 (C_{3a} and C_{7a}), 131.50 ($C_{1'}$), 124.10 ($C_{6'}$), 118.51 (C_5), 117.99 ($C_{3'}$ and $C_{4'}$), 113.05 (C_4), 112.98 (C_6), 111.10 (C_7), 56.41 ($C_{2'}$-OMe), 55.98 ($C_{5'}$-OMe), 21.71 ($-CH_3$). Anal. Calcd for $C_{16}H_{16}N_2O_2$; C: 71.62, H: 6.01, N: 10.44%. Found: C: 71.81, H: 6.23, N: 10.25%.

3.3. 2-(2′-Methoxyphenyl)-5,6-dimethyl-1*H*-benzimidazole (Table 2A, entry 21)

Mp 214–216 °C (EtOAc). IR (KBr): 3258, 2931, 2371, 1585, 1468, 1443, 1384, 1312, 1243, 1023, 857 and 752 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.48 (br s, 1H, –NH), 8.55 (dd, J = 8.1 Hz and 1.7 Hz, 1H, $C_{6'}$–H), 7.37 (one dd and one d merged together, J = 8.6 Hz and 1.8 Hz, 2H, $C_{3'}$–H and $C_{5'}$–H), 7.11 (two doublets merged together as a triplet with a small meta coupling, J = 7.5 Hz and 1.8 Hz, 1H, $C_{4'}$–H), 7.03 and 7.00 (two singlets merged together to form a doublet, 2H, C_4–H and C_7–H), 4.02 (s, 3H, OCH_3), 2.37 [s, 6H, 2 × ($-CH_3$)]. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.58 ($C_{2'}$), 149.01 (C_2, C_{3a} and C_{7a}), 131.43 ($C_{1'}$), 130.72 ($C_{6'}$), 129.94 ($C_{4'}$), 121.62 ($C_{3'}$ and $C_{5'}$), 118.19 (C_5 and C_6), 111.39 (C_4 and C_7), 55.85 (OCH_3), 20.38 [2 × ($-CH_3$)]. Anal. Calcd for $C_{16}H_{16}N_2O$; C: 76.16, H: 6.39, N: 11.10%. Found: C: 76.29, H: 6.23, N: 11.31%.

3.4. 2-(4′-Cyanophenyl)-5,6-dichloro-1*H*-benzimidazole (Table 2A, entry 32)

Mp >320 °C (MeOH). IR (KBr): 3294, 2232, 1610, 1440, 1414, 1291, 1100 and 846 cm^{-1}. ^{1}H NMR [300 MHz, (0.4 mL $CDCl_3$ and 0.1 mL DMSO-d_6)] δ: 12.91 (br s, 1H, –NH), 8.30 (d, J = 8.4 Hz, 2H, $C_{3'}$–H and $C_{5'}$–H), 7.90–7.73 [a br s (for C_4–H) and a doublet (J = 8.4 Hz for $C_{2'}$–H and $C_{6'}$–H) merged together, 3H], 7.61 (br s,



7 (1, 4-di CHO) **1** **8** (1,4-bis-benzimidazole)
9 (1,3-di-CHO) **10** (1,3-bis-benzimidazole)

Scheme 2.

1H, C_7–H). ^{13}C NMR [75 MHz, (0.4 mL $CDCl_3$ and 0.1 mL DMSO-d_6] δ: 150.63 (C_2, C_{3a} and C_{7a}), 132.51 (C_5, C_6 and $C_{1'}$), 131.28 ($C_{3'}$, $C_{5'}$ and C_4), 126.15 ($C_{2'}$, $C_{6'}$ and C_7), 117.04 (CN), 111.79 ($C_{4'}$). Anal. Calcd for $C_{14}H_7N_3Cl_2$; C: 58.36, H: 2.45, N: 14.58%. Found: C: 58.49, H: 2.53, N: 14.66%.

3.5. 5,6-Dichloro-2-[3-(5,6-dichloro-1*H*-benzimidazol-2 yl) phenyl]-1*H*-benzimidazole (Table 3, entry 6)

Mp >320 °C (MeOH). IR (KBr): 3409, 2925, 2856, 2197,1448, 1298, 1098 and 864 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 13.43 [br s, 2H, 2 × (–NH)], 8.96 (s, 1H, $C_{2'}$–H), 8.22 (d, J = 7.7 Hz, 2H, $C_{4'}$–H and $C_{6'}$–H), 8.00–7.62 [m, 5H, (2 × C_4–H), (2 × C_7–H) and $C_{5'}$–H]. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 153.16 (two carbons), 143.44 (two carbons), 134.43 (two carbons), 130.20 (two carbons), 129.86, 128.38 (two carbons), 125.25, 125.02 (two carbons), 124.59 (two carbons), 120.05 (two carbons), 112.99 (two carbons). Anal. Calcd for $C_{20}H_{10}N_4Cl_4$; C: 57.18, H: 2.40, N: 6.67%. Found: C: 57.39, H: 2.44, N: 6.45%.

4. Conclusion

Thus PEG 400 has proved to be a very efficient 'green' promoter for the construction of a wide variety of 2-substituted benzimidazoles and particularly bis-benzimidazoles under catalyst-free and solvent-less conditions at 110 °C (or 140 °C) in excellent yields. This methodology works equally well with both low and high molecular weight PEGs and therefore is a very general and environmentally benign eco-friendly procedure, which would prove beneficial to both academia and industry.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.041.

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