Polyethylene glycol (PEG-400): An efficient medium for the synthesis of 1,2-disubstituted benzimidazoles

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Polyethylene glycol (PEG-400): An efficient medium for the synthesis of 1,2-disubstituted benzimidazoles

Raja Sekhar Mekala¹, Satheesh Krishna Balam¹, Jaya Prakash Soora Harinath¹, Raghavendra Reddy Gajjal¹ and Suresh Reddy Cirandur¹*

Abstract: Polyethylene glycol (PEG-400) was found to be an inexpensive, non-toxic, and effective medium for the one-pot synthesis of 1,2-disubstituted benzimidazoles in excellent yields. Eco-friendliness, low cost, high yields, and recyclability of the PEG-400 are the important features of this protocol.

Subjects: Chemistry; Computational and Theoretical Chemistry; Medicinal & Pharmaceutical Chemistry; Organic Chemistry; Physical Sciences

Keywords: benzimidazoles; PEG-400; one-pot reaction; eco-friendly medium

1. Introduction

Benzimidazoles are very useful intermediates for the development of molecules of pharmaceutical and biological interests. Substituted benzimidazole derivatives have found applications in diverse therapeutic areas including antiulcers, antihypertensives, antivirals, antiinflammatories, anticancers, and antiinfective agents (Kim et al., 1996; Roth et al., 1997; Spasov, Yozhitsa, Bugaeva, & Anisimova, 1999). In addition, they exhibit significant activity against several viruses, such as HIV, herpes (HSV-1), RNA influenza, and human cytomegalovirus (Migawa et al., 1998; Porcari, Devivar, Kucera, Drach, & Townsend, 1998; Tebbe et al., 1997). They have also commercial applications in veterinary medicine (Spasov et al., 1999), as important intermediates in many organic reactions (Bouwman, Driessen, & Reedijk, 1990; Hasegawa et al., 1999), and as ligands to transition metals for modeling biological systems (Pujar & Bharamgoudar, 1988; Zhu et al., 2008). In addition, the treatment potency of benzimidazoles in diseases such as...
ischemia–reperfusion injury (Ogino et al., 2008), hypertension (Shah, Sharma, Bansal, Bansal, & Singh, 2008), obesity (Ghosh & Mandal, 2011), etc. has been recently reported. They also proved to have fungicidal resistance (Delp, 1987, 1988). The important benzimidazole-containing drugs are given in Figure 1.

Owing to their potential biological and other technical interests, a number of synthetic strategies have been developed for their preparation (Dickerson, Reed, & Janda, 2002; Kamal & Reddy, 2005; Suryakiran, Srikanth Reddy, Ashalatha, Laxman, & Venkateswarlu, 2006). Various catalysts such as silica-supported ZnCl₂, (Jacob et al., 2009), LnCl₃, YCl₃ (Li-Jun, Jing, Yong-Qing, Hua, & Shao-Wu, 2012), SBA-15-Supported Poly(4-styrenesulfonyl (perfluorobutylsulfonyl)imide) (Zhong, Sheng, & Jin, 2012), (CH₂)₄SO₃HMIM][HSO₄], a Bronsted Acid Ionic Liquid (Yahya et al., 2010), Thiamine Hydrochloride (Min, Lei, & Lihong, 2012), and Amberlite IR-120 (Mohamed & Aatika, 2012) were engaged for the facile synthesis of benzimidazoles.

In recent years, PEG emerged as a powerful phase-transfer catalyst that performs many useful organic transformations under mild reaction conditions. Moreover, PEG is inexpensive, easy to handle, thermally stable, non-toxic, and recyclable media. Thus, PEG-400 has emerged as an efficient catalyst for various chemical transformations (Chhanda & Tapaswi, 2008; Nagaraju et al., 2015; Nagarapu, Raghu, & Lingappa, 2010; Upendra et al., 2012; Xiaokang, Tangjun, Yu, & Junmin, 2014). We report the synthesis of biologically active benzimidazole derivatives under catalyst-free conditions using PEG-400 as an eco-friendly and recyclable reaction medium.

We studied the PEG-400-mediated synthesis of 3-hydroxy-3-(pyridin-2-ylmethyl)indolin-2-ones (Raghu, Rajasekhar, Reddy, Reddy, & Reddy, 2013), alkyl phosphonates (Mohan Naidu et al., 2011), α-aminophosphonates (Rao, Jayaprakash, Nayak, & Reddy, 2011), α-aminonitriles (Kumar, Babu, Srinivasulu, Kiran, & Reddy, 2007), and its modified catalytic action in the form of PEG-SO₃H for the synthesis of α-aminophosphonates (Reddy et al., 2012) has driven us to explore its application for the study of some other organic compounds. In this hierarchy, we studied the PEG-400-mediated synthesis of 1,2-disubstituted benzimidazoles and accomplished them with good yields.

2. Results and discussion
An efficient and environmentally benign approach was developed for the synthesis of benzimidazole derivatives (3a–m) by reaction of two mol of aldehydes with one mole of substituted benzene 1,2-diamines using PEG-400 as a reaction medium under catalyst-free conditions at 60°C (Scheme 1).

In order to establish the standard operating conditions, the reaction between benzaldehyde with benzene 1,2-diamine was selected as a model reaction. The model reaction is carried out using
PEG-400 as a catalyst at room temperature or 30°C, but there is no sufficient quantity formation of the corresponding benzimidazole derivatives (Table 1, entry 7). Increasing the reaction temperature from 30 to 60°C led to the formation of benzimidazole derivatives up to 86% yield (Table 1, entry 10). Further increase of temperature did not show any improvement in the yields (Table 1, entry 11, 12). In order to compare the rate of the reaction in PEG-400, we carried out the reaction in different solvents (Table 1). It was observed that among the tested solvents, the reaction in PEG-400 was more facile and proceeded to give good yield (86%) when the reaction mixture was stirred at 60°C for 4 h (Table 1, entry 10). Examination of the recyclability of the PEG-400 showed that it can be reused three times without loss of activity (Table 1, entry 10). Moreover, there are many potential advantages of replacing these volatile or toxic organic solvents with PEG-400. Thus, it was established that the reaction carried out in PEG-400 at 60°C was effective for the completion of this reaction, with the above-mentioned parameters being the optimized conditions.

After optimization of the experimental conditions, we extended our studies to various aromatic aldehydes with substituted benzene 1,2-diamines under optimized conditions. In all the cases, reactions were completed within 4.5 h and afforded good to excellent yields (Table 2). Orthophenyldiamine, bearing electron-withdrawing groups (Cl and NO2) at the para position, afforded the desired products in quantitatively high yields. Aromatic aldehydes having both electron-withdrawing and electron-donating groups have no significant effect. Aromatic aldehydes having donating groups require less reaction time when compared to those electron-withdrawing substrates. Results show that the substituents did not play a significant role in governing the overall reaction’s reactivity of the substrates and product yields.

**Table 1. Optimization of reaction conditions for synthesis of 3a**

| Entry | Solvent | Temperature (°C) | Time (h) | Yielda (%) |
|-------|---------|------------------|----------|------------|
| 1     | MeOH    | 60               | 24       | 47         |
| 2     | EtOH    | 60               | 24       | 44         |
| 3     | Toluene | 80               | 24       | 38         |
| 4     | THF     | 60               | 24       | 41         |
| 5     | DMF     | 100              | 24       | 33         |
| 6     | Water   | 80               | 24       | –          |
| 7     | PEG-400 | rt/30            | 6        | 54         |
| 8     | PEG-400 | 40               | 6        | 70         |
| 9     | PEG-400 | 50               | 4        | 77         |
| 10    | PEG-400 | 60               | 4        | 86, 86, 85 |
| 11    | PEG-400 | 70               | 4        | 86         |
| 12    | PEG-400 | 80               | 4        | 85         |

Note: rt denotes room temperature.

aIsolated yields.

bYields with recyclized catalyst.
The chemical structures of all the products were characterized by their analytical and spectral (IR, $^1$H NMR, $^{13}$C NMR, ESIMS, and HRMS) data.

This reaction is facilitated by the nucleophilic attack of the phenylenediamine on the carbonyl carbon in which the electrophilicity of the carbonyl carbon has been enhanced in the PEG-400 medium rather than the other solvents, and hence accelerates the reaction by removing the liberated water, which is soluble in the PEG-400 and enables its conversion to the corresponding benzimidazole (Scheme 2).

### 3. Conclusion

In conclusion, we have developed an efficient and facile eco-friendly method for the synthesis of benzimidazole derivatives by the reaction of $o$-phenylenediamine with aldehydes using PEG-400 as a recyclable reaction medium without the addition of any catalyst or organic co-solvent. The mild reaction conditions, less expensive and recyclable reaction medium, operational simplicity, and high product yields are the advantages of this new protocol.

### 4. Experimental

All the chemicals were purchased from Aldrich and used without further purification. IR spectra were recorded on a Perkin-Elmer 683 Spectrophotometer using KBr optics. $^1$H, $^{13}$C, and $^{31}$P NMR spectra were recorded on Bruker AMX 300 MHz NMR spectrometer in DMSO-$d_6$ using TMS as an internal standard.

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### Table 2. Synthesis of 1,2-disubstituted benzimidazoles

| Entry | $R_1$ | $R_2$ | Time (h) | Yield (%) | mp (°C) |
|-------|-------|-------|----------|-----------|---------|
| 3a    | H     | H     | 4.0      | 86        | 135–137 |
| 3b    | H     | 4-OC$_2$H$_5$ | 4.2     | 85        | 157–159 |
| 3c    | H     | 2-OH  | 4.2      | 83        | 144–146 |
| 3d    | H     | 4-CH$_3$ | 4.3     | 82        | 131–133 |
| 3e    | 3-CH$_3$ | H     | 3.5      | 86        | 159–161 |
| 3f    | 4-Cl  | 4-CH$_3$ | 3.5     | 85        | 138–140 |
| 3g    | 4-Cl  | 4-OCH$_3$ | 3.5     | 87        | 169–171 |
| 3h    | 4-Cl  | H     | 3.5      | 86        | 148–150 |
| 3i    | 4-Cl  | 4-Cl  | 3.8      | 85        | 133–135 |
| 3j    | 4-NO$_2$ | H     | 3.6      | 86        | 175–177 |
| 3k    | 4-NO$_2$ | 4-OC$_2$H$_5$ | 3.5     | 86        | 158–160 |
| 3l    | 4-NO$_2$ | 4-Cl  | 3.2      | 88        | 187–189 |
| 3m    | 4-NO$_2$ | 4-CH$_3$ | 3.5     | 85        | 129–131 |

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Scheme 2. Mechanism for the PEG-mediated synthesis of benzimidazoles.
standard. ESI mass spectra were recorded on a Micromass Quattro LC instrument. Elemental analyses of the synthesized compounds were performed using EA 1112 Thermo Finnigan, France, instrument at University of Hyderabad, Hyderabad, India.

4.1. General procedure for the synthesis of benzimidazole derivative (3a)
A mixture of o-phenylenediamine and benzaldehyde in 1:2 M ratio was taken in 5 ml of polyethylene glycol (PEG-400) and stirred at 60°C for appropriate time. After completion of reaction (TLC), the reaction mixture was cooled and poured in ice cold water. The obtained solid product was filtered and washed with water and recrystallized by ethanol to give pure product 3a. PEG-400 was recovered from water by direct distillation and reused for second run by charging the same substrates (Table 1, entry 10). The above procedure was adopted for the synthesis of the remaining title compounds (3b–m). All the synthesized compounds were obtained in yellow color.

4.2. Spectral data
4.2.1. 1-benzyl-2-phenyl-1H-benzo[d]imidazole (3a)
1H NMR (300 MHz, DMSO-d6): 5.43 (s, 2H), 7.08 (d, 2H Ar), 7.12–7.48 (m, 6H), 7.64 (d, 2H), 7.88 (d, 2H), 8.09 (d, 2H); 13C NMR (75 MHz, DMSO-d6): 47.4, 110.5, 114.9, 119.1, 121.5, 122.5, 123.4, 123.8, 127.5, 127.9, 128.2, 130.2, 130.8, 136.5, 136.9, 142.2, 154.2, 158.5, 160.8; IR (KBr): 3230, 3058, 2923, 1895, 1671, 1599, 1445, 1393, 1360, 1322, 1280, 1168, 1116, 1070, 1026, 994, 928, 738, 773; MS (ESI): m/e 285 (M + H)+. HRMS m/z calc for C20H17N2: 285.1388; found 285.1391.

4.2.2. 1-(4-ethoxybenzyl)-2-(4-ethoxyphenyl)-1H-benzo[d]imidazole (3b)
1H NMR (300 MHz, DMSO-d6): 1.10–1.54 (m, 6H), 3.99–4.49 (m, 4H), 6.89–6.94 (m, 4H), 7.24–7.34 (m, 4H), 7.56–7.59 (m, 6H); 13C NMR (75 MHz, DMSO-d6): 14.2, 14.5, 47.8, 63.5, 114.8, 115.2, 119.5, 121.4, 122.6, 123.5, 123.9, 127.1, 128.2, 128.8, 129.1, 129.8, 130.2, 130.3, 143.8, 147.5, 151.6, 153.8, 158.8, 160.7; IR (KBr): 3429, 2922, 2853, 2854, 1672, 1615, 1585, 1498, 1428, 1396, 1314, 1272, 1222, 1180, 1112, 1015, 960, 871, 818, 741; MS (ESI): m/e 373 (M + H)+. HRMS m/z calc for C24H25N2O2: 373.1931; found 373.1916.

4.2.3. 2-(1-(2-hydroxybenzyl)-1H-benzo[d]imidazol-2-yl)phenol (3c)
1H NMR (300 MHz, DMSO-d6): 5.69 (s, 2H), 7.24–7.34 (m, 6H), 7.54–7.58 (m, 8H); 13C NMR (75 MHz, DMSO-d6): 43.8, 114.5, 115.4, 119.5, 121.1, 122.5, 123.6, 123.9, 127.1, 128.5, 128.9, 129.1, 129.8, 130.2, 136.3, 143.4, 147.8, 151.7, 153.8, 158.5; IR (KBr): 3328, 2821, 2753, 2754, 1688, 1678, 1565, 1546, 1466, 1458, 1378, 1363, 1322, 1187, 1176, 1012, 965, 861, 824, 745; MS (ESI): m/e 317 (M + H)+. HRMS m/z calc for C20H17N2O2: 317.1293; found 317.1290.

4.2.4. 1-(4-methylbenzyl)-2-p-tolyl-1H-benzo[d]imidazole (3d)
1H NMR (300 MHz, DMSO-d6): 2.13 (s, 6H), 5.38 (s, 2H), 6.96–6.95 (d, 2H), 7.06–7.30 (m, 4H), 7.82 (d, 2H), 7.89 (d, 2H), 7.96 (d, 2H); 13C NMR (75 MHz, DMSO-d6): 20.2, 20.5, 51.8, 113.4, 125.6, 125.8, 126.8, 126.7, 127.2, 127.4, 128.7, 128.9, 129.5, 129.8, 130.5, 131.2, 131.7, 138.5, 139.9, 148.2, 149.5, 151.5; IR (KBr): 3429, 2922, 2853, 2854, 1672, 1615, 1585, 1498, 1428, 1396, 1368, 1314, 1270, 1222, 1180, 1112, 1015, 960, 871, 818, 741; MS (ESI): m/e 313 (M + H)+. HRMS m/z calc for C22H21N2: 313.1263; found 313.1268.

4.2.5. 1-benzyl-4-methyl-2-phenyl-1H-benzo[d]imidazole (3e)
1H NMR (300 MHz, DMSO-d6): 1.99 (s, 3H), 5.35 (s, 2H), 7.29–7.31 (m, 6H), 7.59–5.61 (m, 7H); 13C NMR (75 MHz, DMSO-d6): 16.5, 51.5, 108.4, 122.2, 122.7, 123.2, 123.8, 124.1, 125.5, 126.7, 127.7, 128.2, 128.5, 137.1, 137.5, 138.2, 138.7, 139.5, 139.8, 140.5, 151.6; IR (KBr): 3416, 3028, 2923, 2856, 1965, 1599, 1527, 1449, 1393, 1365, 1324, 1276, 1170, 1118, 1068, 1028, 850, 804, 773; MS (ESI): m/e 299 (M + H)+. HRMS m/z calc for C21H19N2: 299.1263; found 299.1268.
4.2.6. 6-chloro-1-(4-methylbenzyl)-2-p-tolyl-1H-benzo[d]imidazole (3f)

1H NMR (300 MHz, DMSO-d6): δ 2.43 (s, 6H), 5.69 (s, 2H), 7.86–7.94 (m, 3H), 7.97–7.99 (m, 4H), 8.20–8.35 (m, 2H), 8.45–8.52 (m, 2H); 13C NMR (75 MHz, DMSO-d6): 20.4, 20.9, 51.2, 11305, 114.2, 114.4, 114.8, 115.5, 115.9, 116.2, 127.4, 125.2, 125.8, 126.2, 126.6, 127.4, 127.8, 128.5, 128.6, 138.8, 139.4, 151.7; IR (KBr): 3317, 3055, 2954, 2756, 1944, 1588, 1533, 1453, 1387, 1365, 1345, 1277, 1199, 1108, 1089, 1044, 850, 804, 775; MS (ESI): m/e 347 (M + H)⁺. HRMS m/z calc for C22H21N2O3 347.1263; found 347.1268.

4.2.7. 6-chloro-1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-1H benzo[d] imidazole (3g)

1H NMR (300 MHz, DMSO-d6): δ 3.82 (s, 6H), 5.35 (s, 2H), 6.79–6.84 (d, 2H), 6.91–7.00 (m, 4H), 7.25–7.35 (d, 2H), 7.45–7.49 (d, 2H), 8.10 (s, 1H); 13C NMR (75 MHz, DMSO-d6): 48.5, 56.3, 114.1, 114.5, 115.3, 115.8, 122.1, 122.4, 127.5, 127.8, 128.2, 128.6, 129.4, 129.7, 130.1, 130.5, 135.2, 135.4, 140.5, 153.6, 158.7, 161.1; IR (KBr): 3315, 3068, 2933, 2922, 1988, 1593, 1545, 1457, 1387, 1375, 1345, 1276, 1160, 1112, 1048, 1028, 855, 805, 763; MS (ESI): m/e 379 (M + H)⁺. HRMS m/z calc for C22H20ClN2O2 398.1553; found 398.1588.

4.2.8. 1-benzyl-6-chloro-2-phenyl-1H-benzo[d]imidazole (3h)

1H NMR (300 MHz, DMSO-d6): δ 5.49 (s, 2H), 6.98–7.10 (d, 2H), 7.11–7.60 (m, 6H), 7.61–7.75 (d, 2H), 7.87 (s, 1H), 7.93–8.01 (d, 2H); 13C NMR (75 MHz, DMSO-d6): 48.2, 113.2, 115.1, 116.7, 124.5, 124.9, 125.1, 125.5, 126.2, 127.5, 127.9, 128.1, 128.5, 129.2, 129.8, 138.2, 138.8, 139.4, 139.9, 151.4; IR (KBr): 3335, 3068, 2933, 2922, 1988, 1593, 1545, 1465, 1335, 1233, 1171, 1276, 1160, 1166, 1067, 1045, 855, 824, 763; MS (ESI): m/e 319 (M + H)⁺. HRMS m/z calc for C20H13ClN2 319.1353; found 313.1366.

4.2.9. 6-chloro-1-(4-chlorobenzyl)-2-(4-chlorophenyl)-1H-benzo[d] imidazole (3i)

1H NMR (300 MHz, DMSO-d6): δ 5.74 (s, 2H), 7.13–7.15 (d, 4H), 7.35–7.36 (d, 3H), 7.58–7.59 (d, 2H), 8.12–8.14 (d, 2H); 13C NMR (75 MHz, DMSO-d6): 50.1, 115.5, 116.9, 124.7, 125.4, 126.5, 127.2, 127.5, 128.2, 128.5, 129.1, 129.6, 130.1, 130.5, 131.3, 131.8, 134.5, 134.8, 141.7, 151.8; IR (KBr): 3336, 3055, 2966, 2866, 1975, 1569, 1522, 1453, 1376, 1335, 1242, 1276, 1130, 1154, 1066, 1018, 854, 802, 753; MS (ESI): m/e 388 (M + H)⁺. HRMS m/z calc for C20H13ClN2O2 388.1546; found 388.1548.

4.2.10. 1-benzyl-6-nitro-2-phenyl-1H-benzo[d]imidazole (3j)

1H NMR (300 MHz, DMSO-d6): δ 5.78 (s, 2H), 7.24–7.34 (m, 6H), 7.65–7.68 (d, 2H) 8.24–8.26 (m, 5H); 13C NMR (75 MHz, DMSO-d6): 51.4, 107.5, 118.7, 125.1, 125.5, 126.5, 127.8, 128.8, 129.1, 130.5, 131.0, 135.5, 135.9, 136.4, 137.6, 137.9, 141.4, 144.0, 147.1, 151.5; IR (KBr): 3376, 3053, 2955, 2845, 1999, 1555, 1534, 1465, 1376, 1345, 1323, 1266, 1178, 1108, 1008, 859, 806, 772; MS (ESI): m/e 330 (M + H)⁺. HRMS m/z calc for C20H13N2O2 330.1266; found 330.1268.

4.2.11. 1-(4-ethoxymethyl)-2-(4-ethoxymethyl)phenyl-6-nitro-1H-benzo[d]imidazole (3k)

1H NMR (300 MHz, DMSO-d6): δ 1.30–1.34 (t, 6H), 5.89–6.94 (d, 4H), 5.78–7.34 (m, 4H), 2.07–2.98 (m, 3H); 13C NMR (75 MHz, DMSO-d6): 20.4, 20.9, 51.2, 107.5, 115.6, 116.3, 116.7, 118.2, 128.1, 128.5, 129.2, 129.6, 131.1, 131.2, 135.3, 135.5, 144.5, 146.8, 148.2, 148.5, 151.2; IR (KBr): 3485, 3376, 2921, 1599, 1490, 1341, 1151, 1093, 976, 896, 871, 819; MS (ESI): m/e 398 (M + H)⁺. HRMS m/z calc for C20H13ClN2O2 398.1553; found 398.1588.
1H NMR (300 MHz, DMSO-d6): δ 2.36 (s, 6H), 5.78 (s, 2H), 7.15–7.18 (d, 4H), 7.28–7.30 (d, 2H), 7.66–7.69 (d, 2H), 7.99–8.12 (m, 3H); 13C NMR (75 MHz, DMSO-d6): 14.4, 17.1, 21.2, 106.5, 125.3, 126.7, 123.5, 127.5, 127.7, 129.5, 137.2, 137.6, 138.4, 139.8, 140.4, 140.8, 141.2, 142.5, 142.7, 145.5, 152.6, 156.2; IR (KBr): 3234, 2923, 1621, 1550, 1446, 1146, 1183, 1120, 1062, 882, 819, 736; MS (ESI): m/e 358 (M + H)+. HRMS m/z calc for C22H20N3 O2 358.1463; found 358.1468.

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Note
Working on the synthesis of Organophosphorus Chemistry since 1990 as a successor scientist of Dr. C. Devendranath Reddy, who paved the way for Organophosphorus Chemistry research in the Department of Chemistry, Sri Venkateswara University, Tirupati, India.

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