Poly(ethyleneglycol): A Versatile and Recyclable Reaction Medium in Gaining Access to Benzo[4,5]imidazo[1,2-*a*]pyrimidines Under Microwave Heating

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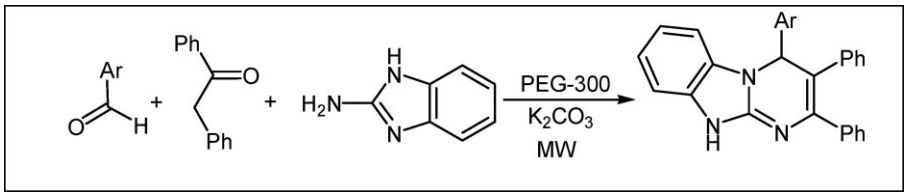

Polyethylene glycol is found to be a nontoxic and recyclable reaction medium for the microwave-assisted, one-pot, multicomponent reactions of aromatic aldehydes with 2-aminobenzimidazole and 1,2-diphenylethanone in the presence of potassium carbonate. This environmentally friendly microwave protocol offers ease of operation and enables recyclability of reaction media and synthesis of a variety of substituted benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives. It is an efficient, promising, and green synthetic strategy to construct benzo[4,5]imidazo[1,2-*a*]pyrimidine skeleton.

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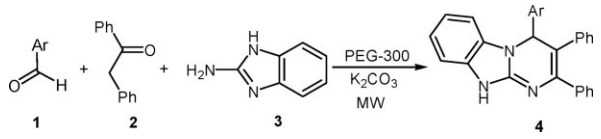
INTRODUCTION

The search for alternative reaction media to replace volatile and often toxic solvents commonly used in organic synthetic procedures is an important objective of significant environmental consequence [1]. Media considered include (a) the use of supercritical fluids [2] that have the advantage of facile solvent removal and easy recyclability but require high pressure; (b) fluorous-based systems [3] that have the advantage of being highly hydrophobic but expensive and for which the solvents are probably innocuous but have the disadvantage of being volatile; (c) more recently, environmentally benign solvents such as ionic liquids [4] and water [5]. Ionic liquids have a particularly useful set of properties, being nonvolatile and readily dissolving many transition metal catalysts but their preparation was not convenient, and volatile organic solvents were also used for the preparation. The use of water as solvent is probably the most desirable approach, but this is often not possible due to the hydrophobic nature of the reactants. It is customary to measure the efficiency of a catalyst by the number of cycles for which it can be reused. Similarly, the value of a new solvent medium primarily depends on its environmental impact, the ease with which it can be recycled, low vapor pressure, nonflammability, and high polarity for solubilization. In performing the majority of organic transformations, solvents play an important role in mixing the ingredients to make the system homogeneous and allow molecular interactions to be more efficient [6].

Recently, using polyethylene glycol (PEG) as a green reaction medium has become an important research area [7]. In addition to be a safe, readily available, and environmentally friendly solvent [8], PEG has also been recognized as an effective and recyclable reaction medium with unique properties and potentials for many organic reactions such as substitution, oxidation, and reduction. Under microwave irradiation (MW), PEG is rapidly heated to high temperature, enhancing molecular interactions more efficiently. Thus, it is clear that the combined approach of microwave superheating and PEG as a reaction medium could be considered a promising and green synthetic strategy for the construction of important heterocyclic skeleton.

Imidazo[1,2-*a*]pyrimidines are well-known compounds because of their pharmacological profiles as anti-cytomegalo-zoster and antivaricella-zoster virus [9]. The chemical modification of the imidazopyrimidine ring such as the introduction of different substituents or heteroatoms have allowed expansion of the research to structure–activity relationship to afford new insight into the molecular interaction at the receptor level. With an imidazo[1,2-*a*]pyrimidine parent nucleus, benzo[4,5] imidazo[1,2-*a*]pyrimidine derivatives showed a diverse range of biological properties such as antineoplastic activity [10], and acted as C3a receptor antagonists [11]

Scheme 1

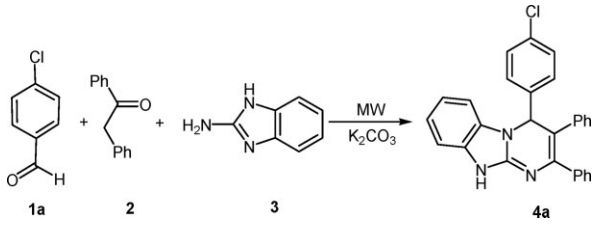


and new calcium antagonists [12]. Because of a range of biological activity they exhibited, these compounds have distinguished themselves as heterocycles of profound chemical and biological significance. Thus, the synthesis of these molecules has attracted considerable attention [13]. Recently, the synthesis of benzo[4,5] imidazo[1,2-*a*]pyrimidine derivatives were reported by Alvarez-Builla and coworkers *via* the reaction of an requisite arylmethyleneacetoacetate with 2-aminobenzimidazole [14]. The improved procedure for benzo[4,5]-imidazo[1,2-*a*]pyrimidines in ionic liquid through the condensation of aldehydes with β-ketoester and 2-aminobenzimidazole was described by Shaabani *et al*. [15]. However, the synthesis of new heterocyclic compounds containing benzoimidazopyrimidine scaffold and development of more rapid and efficient entry to this heterocycles are strongly desired. In connection with our previous studies [16], to modify benzoimidazopyrimidine scaffold, in this article we report a practical, inexpensive, rapid, and green microwave-promoted method for the synthesis of new heterocyclic compounds containing benzoimidazopyrimidine unit in PEG-300 using 1,2-diphenylethanone as potent precursor (Scheme 1).

RESULTS AND DISCUSSION

2-Aminobenzimidazole is a versatile and readily obtainable reagent, and its chemistry has received considerable attention in recent years due to the high nucleophilic reactivity of two nitrogen atoms [17]. Our strategy synthesizing the poly-substituted benzo[4,5]imidazo[1,2-*a*]pyrimidines was that 2-aminobenzimidazole was examined as starting material to react with aromatic aldehydes and 1,2-diphenylethanone under microwave heating. Initially, we screened various conditions for the one-pot, three-component reaction of equimolar amount of 2-aminobenzimidazole with 4-chlorobenzaldehyde and 1,2-diphenylethanone at 100°C in the presence of potassium carbonate under microwave irradiation (Scheme 2 and Table 1). Among various polar solvents tested, glacial acetic acid (HOAc), acetonitrile, ethanol, and water gave poor to moderate yields of the expected product (Table 1, entries 1−4). The best solvent was found to be PEG-300. In this solvent, benzo[4,5]imidazo[1,2-*a*]pyrimidines (**4a**) was obtained with the best yield (Table 1, entry 5). To further optimize the reaction conditions, the reaction was carried out at temperatures

Scheme 2



ranging from 90 to 130°C, with an increment of 10°C each time. The yield of product **4a** was increased and the reaction time was shortened as the temperature was increased from 90 to 120°C (Table 1, entries 5−8). However, further increase of the temperature to 130°C failed to improve the yield of product **4a** (Table 1, entry 9). Therefore, 120°C was chosen as the reaction temperature for all further microwave-assisted reactions.

The use of these optimal microwave experimental conditions [PEG-300, 120°C] to the reactions of different aromatic aldehydes afforded good yields of benzo[4,5]imidazo[1,2-*a*]pyrimidines, with two phenyl groups presenting in positions 4 and 5 of the new forming pyrimidine nucleus, respectively. To test the scope of aromatic aldehydes, 2-aminobenzimidazole and 1,2-diphenylethanone were used as model substrates, and the results (Table 2, entries 1–11) indicated that aromatic aldehydes bearing functional groups such as chloro, bromo, or methoxy are suitable for the reaction. We have also observed electronic effects, that is, aromatic aldehydes with electron-withdrawing groups (Table 2, entries 1−4) reacted rapidly, while electron-rich groups (Table 2, entries 6−11) decreased the reactivity, requiring longer reaction times.

The use of PEG as a recyclable reaction medium in these reactions avoids the use of volatile and toxic organic solvents. In addition to the often referred advantages of using PEG-300 as solvent, this procedure has following remarkable features when compared to conventional method: (1) short reaction time, (2) clean reaction protocol, (3) high yielding.

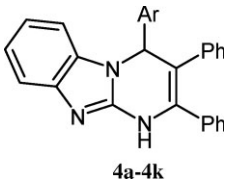
Table 1

Optimization for the synthesis of **4a** under MW.

Entry	Solvent	*T* (°C)	Time (min)	Yield (%)
1	HOAc	100	10	46
2	CH_3CN	100	10	34
3	Ethanol	100	10	57
4	Water	100	10	41
5	PEG-300	100	10	68
6	PEG-300	90	14	60
7	PEG-300	110	12	76
8	PEG-300	120	12	87
9	PEG-300	130	12	83

Table 2

Synthesis of compounds **4** under microwave irradiation.

Entry	Product	Ar	Time (min)	Yield (%)	mp (°C)
1	 **4a-4k**	**4a**, 4-Chlorophenyl (**1a**)	12	87	284–286
2		**4b**, 4-Bromophenyl (**1b**)	12	85	>300
3		**4c**, 2-Chlorophenyl (**1c**)	10	86	>300
4		**4d**, 2,4-Dichlorophenyl (**1d**)	10	84	>300
5		**4e**, Phenyl (**1e**)	14	82	274–276
6		**4f**, 4-Tolyl (**1f**)	14	80	295–297
7		**4g**, 4-Dimethylaminophenyl (**1g**)	16	78	>300
8		**4h**, Benzo[*d*][1,3]dioxol-5-yl (**1h**)	14	80	>300
9		**4i**, 4-Methoxyphenyl (**1i**)	14	79	250–252
10		**4j**, 3,4-Dimethoxyphenyl (**1j**)	16	75	267–268
11		**4k**, 3,4,5-Trimethoxyphenyl (**1k**)	18	76	296–298

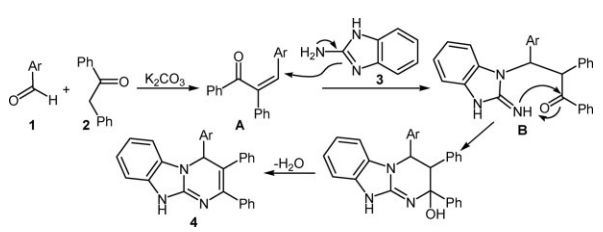
To prove that the use of PEG as solvent is practical, it has to be conveniently recyclable with minimal loss and decomposition. Because PEG is immiscible with aliphatic hydrocarbons, the desired product may be extracted with compounds such as cyclohexane [18], and the retained PEG phase may be reused. In the recycling study, the reaction between 4-chlorobenzaldehyde, 1,2-diphenylethanone, and 2-aminobenzimidazole in the presence of potassium carbonate could be repeated three times without reduction of the yield (84% ± 3%), although a weight loss of ~10% PEG was observed from cycle to cycle.

The formation of **4** is likely to proceed *via* initial condensation of aromatic aldehydes **1** with 1,2-diphenylethanone **2** to afford 3-aryl-1,2-diphenylprop-2-en-1-one **A,** which further undergoes *in situ* Michael addition reaction with 2-aminobenzimidazole **3** to yield intermediate **B**. The intermediate **B** is upon intramolecular cyclization and dehydration to generate final products 4 (Scheme 3).

In this study, all the products were characterized by melting point, IR, and ^{1}H NMR spectral data, as well as elemental analysis.

In conclusion, we have demonstrated that PEG is a convenient, inexpensive, nonionic liquid, nontoxic, and recyclable reaction medium for the efficient synthesis of 4,5-bis-aryl substituted benzo[4,5]imidazo[1,2-*a*]pyrimidines. Interestingly, we found a new multicomponent reaction of aromatic aldehydes with 1,2-diphenylethanone and 2-aminobenzimidazole in PEG-300, which provides a rapid and efficient route for the construction of benzo[4,5]imidazo[1,2-*a*]pyrimidine skeleton. This protocol offers a rapid and clean alternative and reduces reaction time. The recyclability of the reaction media makes reaction economically and potentially viable for commercial applications.

Scheme 3



EXPERIMENTAL

Microwave irradiation was carried out with a microwave oven Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in the open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^{1}H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analysis was determined by using a Perkin-Elmer 240c elemental analysis instrument.

General procedure for the one-pot synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives under microwave irradiation conditions. Typically, in a 10-mL Emrys™ reaction vial, aromatic aldehyde 1 (1 mmol), 1,2-diphenylethanone 2 (1 mmol), 2-aminobenzimidazole 3 (1 mmol), potassium carbonate (0.4 mmol), and PEG-300 (2 mL) were mixed and then capped. The mixture was irradiated for a given time at 120°C under microwave irradiation (initial power 100 W and maximum power 250 W). Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature. The precipitated product was filtered off and the filter liquor was extracted by diethyl ether. The residue left after evaporation of the solvent was added to the solid product isolated by filtration, and purified by flash chromatography (silica gel, petroleum ether: acetone = 10:1) to give rise to the pure product 4. The recovered PEG can be reused for a number of cycles without significant loss of activity.

4-(4-Chlorophenyl)-2,3-diphenyl-4,10-dihydrobenzo[4,5]-imidazo[1,2-*a*]pyrimidine (4a). ir (potassium bromide): 3055, 3025, 2820, 1625, 1578, 1408, 1279, 1088, 1011, 830, 774, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.22 (s, 1H, NH), 7.40 (d, 2H, J = 8.4 Hz, ArH), 7.31 (d, 2H, J = 8.8 Hz, ArH), 7.26–7.24 (m, 6H, ArH), 7.15 (d, 1H, J = 8.0 Hz, ArH), 7.07–7.00 (m, 4H, ArH), 6.91–6.88 (m, 3H, ArH), 6.66

(s, 1H, CH). Anal. calcd. for $C_{28}H_{20}ClN_3$: C, 77.50; H, 4.65; N, 9.68. Found: C, 77.31; H, 4.67; N, 9.55.

4-(4-Bromophenyl)-2,3-diphenyl-4,10-dihydrobenzo[4,5]-imidazo[1,2-*a*]pyrimidine (4b). ir (potassium bromide): 3054, 3024, 2820, 1626, 1579, 1403, 1286, 1071, 1009, 841, 774, 699 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.19 (s, 1H, NH), 7.45 (d, 2H, J = 8.0 Hz, ArH), 7.33 (d, 2H, J = 8.4 Hz, ArH), 7.30–7.27 (m, 6H, ArH), 7.15 (d, 1H, J = 8.0 Hz, ArH), 7.07–7.00 (m, 4H, ArH), 6.92–6.89 (m, 3H, ArH), 6.65 (s, 1H, CH). Anal. calcd. for $C_{28}H_{20}BrN_3$: C, 70.30; H, 4.21; N, 8.78. Found: C, 70.46; H, 4.19; N, 8.69.

4-(2-Chlorophenyl)-2,3-diphenyl-4,10-dihydrobenzo[4,5]-imidazo[1,2-*a*]pyrimidine (4c). ir (potassium bromide): 3051, 3023, 2822, 1627, 1579, 1459, 1283, 1034, 913, 783, 697 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.25 (s, 1H, NH), 7.52 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.6 Hz, ArH), 7.28–7.24 (m, 8H, ArH), 7.18 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.6 Hz, ArH), 7.03–6.96 (m, 5H, ArH), 6.92–6.87 (m, 3H, ArH), 6.85 (s, 1H, CH). Anal. calcd. for $C_{28}H_{20}ClN_3$: C, 77.50; H, 4.65; N, 9.68. Found: C, 77.59; H, 4.64; N, 9.74.

4-(2,4-Dichlorophenyl)-2,3-diphenyl-4,10-dihydrobenzo [4,5]-imidazo[1,2-*a*]pyrimidine (4d). ir (potassium bromide): 3055, 3024, 2816, 1626, 1580, 1459, 1282, 1102, 1010, 843, 772, 696 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.25 (s, 1H, NH), 7.54 (d, 1H, J = 8.4 Hz, ArH), 7.45 (s, 1H, ArH), 7.34 (d, 1H, J = 8.0 Hz, ArH), 7.29 (d, 1H, J = 8.0 Hz, ArH), 7.24 (s, 5H, ArH), 7.04–6.97 (m, 5H, ArH), 6.93–6.89 (m, 3H, ArH), 6.88(s, 1H, CH). Anal. calcd. for $C_{28}H_{19}Cl_2N_3$: C, 71.80; H, 4.09; N, 8.97. Found: C, 71.72; H, 4.11; N, 8.90.

2,3,4-Triphenyl-4,10-dihydrobenzo[4,5]imidazo[1,2-*a*]-pyrimidine (4e). ir (potassium bromide): 3053, 3023, 2823, 1626, 1509, 1458, 1284, 1073, 829, 782, 700 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.14 (s, 1H, NH), 7.39(d, 2H, J = 7.2 Hz, ArH), 7.29–7.27 (m, 3H, ArH), 7.26–7.23 (m, 5H, ArH), 7.17 (d, 2H, J = 7.2 Hz, ArH), 7.05–6.98 (m, 4H, ArH), 6.90–6.87 (m, 3H, ArH), 6.57 (s, 1H, CH). Anal. calcd. for $C_{28}H_{21}N_3$: C, 84.18; H, 5.30; N, 10.52. Found: C, 84.24; H, 5.33; N, 10.49.

4-*p*-Tolyl-2,3-diphenyl-4,10-dihydrobenzo[4,5]imidazo-[1,2-*a*]pyrimidine (4f). ir (potassium bromide): 3051, 3022, 2825, 1626, 1574, 1459, 1282, 1179, 1009, 826, 774, 698 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.12 (s, 1H, NH), 7.29 (d, 2H, J = 8.0 Hz, ArH), 7.28–7.21 (m, 6H, ArH), 7.18 (d, 1H, J = 8.0 Hz, ArH), 7.06 (d, 2H, J = 7.6 Hz, ArH), 7.03–6.98 (m, 4H, ArH), 6.90–6.87 (m, 3H, ArH), 6.53 (s, 1H, CH), 2.18 (s, 3H, CH_3). Anal. calcd. for $C_{29}H_{23}N_3$: C, 84.23; H, 5.61; N, 10.16. Found: C, 84.31; H, 5.59; N, 10.21.

4-(4-Dimethylaminophenyl)-2,3-diphenyl-4,10-dihydro-benzo [4,5]imidazo[1,2-*a*]pyrimidine (4g). ir (potassium bromide): 3053, 3023, 2802, 1625, 1575, 1444, 1234, 1165, 1073, 827, 777, 698 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.05 (s, 1H, NH), 7.26–7.23 (m, 9H, ArH), 7.05–6.97 (m, 4H, ArH), 6.91–6.87 (m, 3H, ArH), 6.58 (d, 2H, J = 8.4 Hz, ArH), 6.39 (s, 1H, CH), 2.81 (s, 6H, CH_3). Anal. calcd. for $C_{30}H_{26}N_4$: C, 81.42; H, 5.92; N, 12.66. Found: C, 81.34; H, 5.95; N, 12.72.

4-Benzo[1,3]dioxol-5-yl-2,3-diphenyl-4,10-dihydrobenzo[4,5]-imidazo[1,2-*a*]pyrimidine (4h). ir (potassium bromide): 3051, 3018, 2824, 1627, 1573, 1460, 1237, 1039, 935, 853, 777, 698 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.13 (s, 1H, NH), 7.29–7.27 (m, 2H, ArH), 7.26–7.23 (m, 5H, ArH), 7.07–6.99 (m, 4H, ArH), 6.94–6.89 (m, 5H, ArH), 6.78 (d, 1H, J = 8.4 Hz, ArH), 6.50 (s, 1H, CH), 5.93 (d, 2H, J = 16 Hz, CH_2). Anal. calcd. for $C_{29}H_{21}N_3O_2$: C, 78.54; H, 4.77; N, 9.47. Found: C, 78.62; H, 4.75; N, 9.53.

4-(4-Methoxyphenyl)-2,3-diphenyl-4,10-dihydrobenzo[4,5]-imidazo[1,2-*a*]pyrimidine (4i). ir (potassium bromide): 3048, 3016, 2834, 1628, 1580, 1418, 1264, 1028, 856, 777, 701 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.14 (s, 1H, NH), 7.35 (d, 2H, J = 8.8 Hz, ArH), 7.29–7.26 (m, 5H, ArH), 7.25–7.20 (m, 2H, ArH), 7.06–6.98 (m, 4H, ArH), 6.91–6.87 (m, 3H, ArH), 6.81 (d, 2H, J = 8.8 Hz, ArH), 6.51 (s, 1H, CH), 3.65 (s, 3H, OCH_3). Anal. calcd. for $C_{29}H_{23}N_3O$: C, 81.09; H, 5.40; N, 9.78. Found: C, C, 81.01; H, 5.43; N, 9.69.

4-(3,4-Dimethoxyphenyl)-2,3-diphenyl-4,10-dihydrobenzo [4,5]imidazo[1,2-*a*]pyrimidine (4j). ir (potassium bromide): 3048, 3016, 2834, 1628, 1580, 1418, 1264, 1028, 856, 777, 701 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.09 (s, 1H, NH), 7.29–7.25 (m, 7H, ArH), 7.07–7.01 (m, 4H, ArH), 7.00–6.96 (m, 2H, ArH), 6.95–6.93 (m, 1H, ArH), 6.90 (d, 2H, J = 8.0 Hz, ArH), 6.84 (d, 1H, J = 8.4 Hz, ArH), 6.48 (s, 1H, CH), 3.65 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3). Anal. calcd. for $C_{30}H_{25}N_3O_2$: C, 78.41; H, 5.48; N, 9.14. Found: C, 78.52; H, 5.46; N, 9.20.

4-(3,4,5-Trimethoxyphenyl)-2,3-diphenyl-4,10-dihydrobenzo [4,5]imidazo[1,2-*a*]pyrimidine (4k). ir (potassium bromide): 3050, 3018, 2834, 1651, 1571, 1418, 1251, 1125, 1011, 828, 779, 701 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.13 (s, 1H, NH), 7.41 (d, 1H, J = 7.6 Hz, ArH), 7.30–7.28 (m, 6H, ArH), 7.08–7.01 (m, 4H, ArH), 6.96 (d, 1H, J = 7.6 Hz, ArH), 6.91 (d, 2H, J = 7.6 Hz, ArH), 6.78 (s, 2H, ArH), 6.47 (s, 1H, CH), 3.66 (s, 6H, OCH_3), 3.56 (s, 3H, OCH_3). Anal. calcd. for $C_{31}H_{27}N_3O_3$: C, 76.05; H, 5.56; N, 8.58. Found: 76.13; H, 5.54; N, 8.63.

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