Green Multicomponent Synthesis of 1,2-Dihydro-pyrimido[1,2-*a*]-benzimidazole-3-carbonitrile

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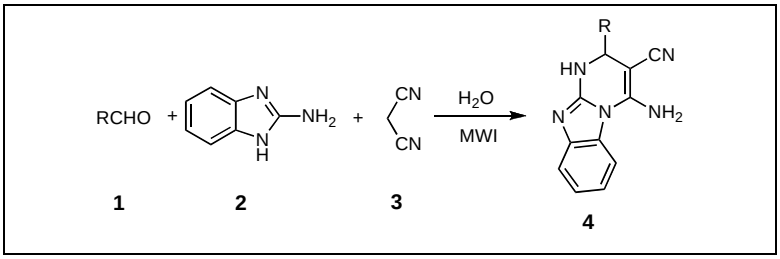

1,2-dihydro-pyrimido[1,2-*a*]benzimidazole-3-carbonitrile derivatives were synthesized *via* the three-component reaction of aldehyde, malonodinitrile and 2-aminobenzimidazole in water under microwave irradiation. The new protocol has the advantages of excellent yield, low cost, reduced environment impact, wide scope and convenient procedure.

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INTRODUCTION

As early as in the 1980s Breslow demonstrated that hydrophobic effects could strongly enhance the rate of some organic reactions and rediscovered the use of water as solvent in organic chemistry [1,2]. Since then, the use of water as a solvent has attracted considerable research interest [3-5]. Water, compared with organic solvents, is abundant, nontoxic and environment-friendly. Therefore, it has become an attractive medium for many organic reactions [6-8], not only for the advantages concerning the avoidance of expensive drying reactants, catalysts and solvents, but also for some unique reactivity and selectivity [9-12]. Furthermore, organic reactions in water without using harmful organic solvents is one of the current focuses today especially in the environmentally conscious society.

The rapid assembly of molecular diversity is an important goal of synthetic organic chemistry and one of the key paradigms of modern drug discovery [13,14]. One approach to address this challenge involves the development of multicomponent reactions (MCRs), in which three or more reactants are combined together in a single reaction flask to generate a product incorporating most of the atoms contained in the starting materials [15,16]. Diversity can be achieved by simply varying each component or just changing the reaction conditions [17,18]. In addition to the intrinsic atom economy and selectivity underlying such reactions, simpler procedures and equipment, time, and energy savings, as well as environmental friendliness have all led to a sizable effort to design and implement MCRs in both academia and industry [19].

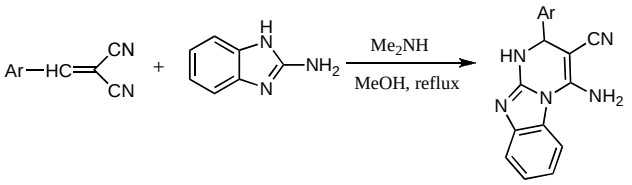
Microwave (MW) assisted organic synthesis has been a topic of continued studies as it could lead to higher yields of pure products, easier operation and shorter reaction time as compared to traditional heating methods [20-23]. Use of MW irradiation for the formation of carbon-heteroatoms, especially carbon-nitrogen bonds, has been reported [24-28]. This study is a continuation of our earlier work [29,30], in which we have shown green methods for the formation of heterocyclic compounds containing the nitrogen atom.

Much attention has been devoted towards dihydro-pyrimidine derivatives due to their significant therapeutic and medicinal properties [31-33]. Several marine alkaloids having the dihydropyrimidine core unit were found to show interesting biological activities such as antiviral, antibacterial and anti-inflammatory activities [34,35]. Many functionalized derivatives are used as calcium channel blockers, antihypertensive agents and α-la antagonists [36,37]. Therefore, the preparation of this heterocyclic core unit has gained much importance.

2-Aminobenzimidazole has been used as material in the synthesis of many kinds of compounds [38]

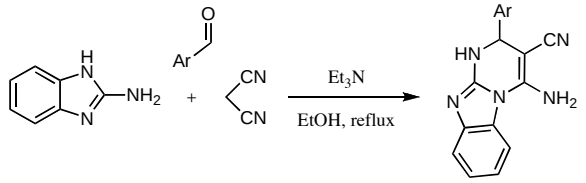
Sergey A. Komykhov [39] and co-workers reported the reaction of α,β-unsaturated nitrile with 2-aminobenz-imidazole to get 1,2-dihydro-benzo[4,5]imidazo[1,2-*a*]-pyrimidine-3-carbonitrile derivatives. Their protocol performed the reactions in ethanol with Me_2NH catalyst and yields of around 30%-40% (Scheme 1).

Scheme 1



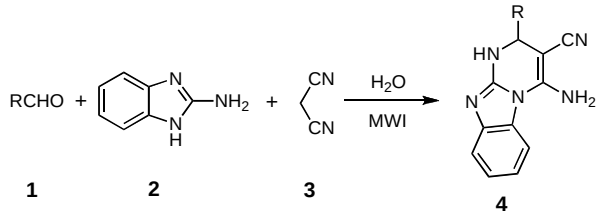
Braulio Insuasty [40] and co-workers have reported the reaction of aromatic aldehyde, 2-aminobenzimidazole and malonodinitrile in ethanol (Scheme 2). Their protocol has the advantages of less toxic solvent and higher yields (50%-60%). However, their reactions needed triethylamine as catalyst.

Scheme 2



Therefore we wish to report a facile, rapid and green protocol for the three component condensation reaction of an aldehyde, malonodinitrile and 2-aminobenzimidazole in water under microwave irradiation without catalyst (Scheme 3).

Scheme 3



RESULTS AND DISCUSSION

Choosing an appropriate solvent is of crucial importance for successful MW promoted synthesis. In order to search for the best condition for this reaction, the MW assisted reaction of 4-chlorobenzaldehyde (**1a**), malonodinitrile and 2-aminobenzimidazole was examined in various volume proportions of EtOH and H_2O, with the total volume of 2 mL, at 80°C. All the reactions were carried out with 200 W of power. The results are summarized in Table 1.

As shown in Table 1, to our delighted, with all the volume of water as solvent, satisfying result were obtained. Water was used as the solvent for all further microwave-assisted reactions as it is also environmentally friendly and the use of expensive organic reagents can be avoided.

Table 1.
Solvent Optimization for the Synthesis of **4a** under MWI at 80 °C

Entry	X/Y	Power / W	Time / min	Yield / %
1	10(X)	200	4	91
2	8/2	200	5	91
3	6/4	200	5	90
4	4/6	200	5	91
5	2/8	200	4	90
6	10(Y)	200	4	91

X=EtOH, Y=H_2O; Volume proportion

Microwave irradiation power and temperature were also optimized for the synthesis of **4a**. The most suitable irradiation power was 200 W and temperature was 80 °C.

Based on these optimized reaction conditions, a series of 1,2-dihydro-pyrimido[1,2-*a*]benzimidazole-3-carbonitrile derivatives were synthesized. The results are summarized in Table 2.

As shown in Table 2, this protocol could be applied not only to the aromatic aldehydes with either electron-withdrawing groups or electron-donating groups, but also to aliphatic aldehydes, which highlighted the wide scope of this three-component condensation. Furthermore, the procedure is easy to operate and the workup procedure is just simple filtration.

Moreover, we performed the synthesis of **4a** with water as solvent under both MWI and classical heating conditions. The reaction was efficiently promoted by MWI and the reaction time was strikingly shortened to 5 min from 2.5 h required under traditional heating condition and the yield was increased to 91% from 45%. Therefore, microwave irradiation exhibited several advantages over the conventional heating by significantly reducing the reaction time and dramatically improving the reaction yield owing to a specific nonthermal microwave effect [41].

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

In conclusion, we have developed a three-component reaction of an aldehyde, malonodinitrile and 2-aminobenzimidazole in water under microwave irradiation conditions for the synthesis of 1,2-dihydro-pyrimido[1,2-*a*]benzimidazole-3-carbonitrile derivatives. Particularly valuable features of this method include excellent yields of the products, shorter reaction time, reduced environmental impact, and straightforward procedure.

EXPERIMENTAL

Microwave irradiation was carried out in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a TENSOR 27 spectrometer in KBr. ^{1}H NMR spectra were measured on a DPX 400 spectrometer operating at 400 MHz, using DMSO-d_6 as solvent and TMS as internal standard. Elemental analyses were performed by using a Perkin-Elmer 240c elemental analysis instrument.

Table 2

Synthesis of **4** in water under Microwave Irradiation Conditions at 80 °C

Entry	4	R	Time(min)	Yield(%)(lit)	Mp(°C)
1	**4a**	4-ClC_6H_4	5	91(37)[38](60)[39]	241-242(232decomp)[38](238)[39]
2	**4b**	C_6H_5	5	90(45)[38](55)[39]	230-233(205-207)[38](218)[39]
3	**4c**	4-BrC_6H_4	4	91(60)[39]	240-242(209)[39]
4	**4d**	2-ClC_6H_4	5	89	242-243
5	**4e**	4-FC_6H_4	4	91	246-248
6	**4f**	2,4-$Cl_2C_6H_3$	4	94	255-256
7	**4g**	4-$CH_3OC_6H_4$	5	89(30)[38](50)[39]	230-233(212-213)[38](197)[39]
8	**4h**	3,4-$(CH_3O)_2C_6H_3$	5	88	246-249
9	**4i**	3,4,5-$(CH_3O)_3C_6H_2$	6	90(60)[39]	247-248(225)[39]
10	**4j**	4-$CH_3C_6H_4$	5	92	238-239
11	**4h**	n-C_4H_9	6	84	220-223

General Procedure for the synthesis of 1,2-dihydropyrimido[1,2-*a*]benzimidazole-3-carbonitrile derivatives (4a-4j). In a 10 mL Emrys™ reaction vial, aldehyde (1 mmol), malonodinitrile (1 mmol), 2-aminobenzimidazole (1 mmol) and water (2 mL) were mixed and then capped. After irradiation for 4-6 min, the reaction mixture was cooled to room temperature. Then the solid was collected by filtration give crude product, which was further purified by recrystallized from 95% EtOH.

4-Amino-2-(4-chlorophenyl)-1,2-dihydropyrimido[1,2-*a*]-benzimidazole-3-carbonitrile (4a). This compound was obtained according to above general procedure; ir (potassium bromide): 3420, 3326, 3214, 3058, 2884, 2188, 1677, 1598, 1468, 738 cm^{-1}; ^1H nmr: δ 8.60 (s, 1H, NH), 7.63 (d, 1H, J = 8.0 Hz, ArH), 7.43 (d, 2H, J = 8.8 Hz, ArH), 7.31 (d, 2H, J = 8.4 Hz, ArH), 7.24 (d, 1H, J = 7.6, ArH), 7.12 (t, 1H, J = 7.6 Hz, ArH), 7.01 (t, 1H, J = 7.6 Hz, ArH), 6.89 (s, 2H, NH_2), 5.26 (s, 1H, CH). *Anal* calcd. for $C_{17}H_{12}ClN_5$: C, 63.46; H, 3.76; N, 21.77. Found: C, 63.39; H, 3.75; N, 21.65.

4-Amino-2-phenyl-1,2-dihydropyrimido[1,2-*a*]benzimidazole-3-carbonitrile (**4b**). This compound was obtained according to above general procedure; ir (potassium bromide): 3444, 3321, 3217, 3057, 2877, 2189, 1682, 1601, 1440, 1310, 1026, 816, 751 cm^{-1}; ^1H nmr: δ 8.59 (s, 1H, NH), 7.61 (d, 1H, J = 8.0 Hz, ArH), 7.37-7.23 (m, 6H, ArH), 7.12 (t, 1H, J = 7.2 Hz, ArH), 7.01 (t, 1H, J = 8.0 Hz, ArH), 6.84 (s, 2H, NH_2), 5.21 (s, 1H, CH). *Anal* calcd. for $C_{17}H_{13}N_5$: C, 71.06; H, 4.56; N, 24.37. Found: C, 71.73; H, 4.55; N, 24.43.

4-Amino-2-(4-bromophenyl)-1,2-dihydropyrimido[1,2-*a*]-benzimidazole-3-carbonitrile (4c). This compound was obtained according to above general procedure; ir (potassium bromide): 3423, 3325, 3213, 3057, 2905, 2187, 1676, 1597, 1467, 1245, 829, 737 cm^{-1}; ^1H nmr: δ 8.61 (s, 1H, NH), 7.64-7.56 (m, 3H, ArH), 7.26-7.23 (m, 3H, ArH), 7.12 (t, 1H, J = 7.2 Hz, ArH), 7.01 (t, 1H, J = 7.6 Hz, ArH), 6.89 (s, 2H, NH_2), 5.23 (s, 1H, CH). *Anal* calcd. for $C_{17}H_{12}BrN_5$: C, 55.75; H, 3.30; N, 19.15. Found: C, 55.86; H, 3.31; N, 19.22.

4-Amino-2-(2-chlorophenyl)-1,2-dihydropyrimido[1,2-*a*]-benzimidazole-3-carbonitrile (4d). This compound was obtained according to above general procedure; ir (potassium bromide): 3426, 3313, 3208, 3058, 2896, 2198, 1678, 1630, 1599, 1443, 1242, 1061, 950, 817, 739 cm^{-1}; ^1H nmr: δ 8.50 (s, 1H, NH), 7.67 (d, 1H, J = 8.0 Hz, ArH), 7.50-7.48 (m, 1H, ArH), 7.35-7.34 (m, 3H, ArH), 7.25 (d, 1H, J = 8.0 Hz, ArH), 7.14 (t, 1H, J = 7.2 Hz, ArH), 7.03 (t, 1H, J = 7.6 Hz, ArH), 6.90 (s, 2H, NH_2), 5.64 (s, 1H, CH). *Anal* calcd. for $C_{17}H_{12}ClN_5$: C, 63.46; H, 3.76; N, 21.77. Found: C, 63.38; H, 3.77; N, 21.69.

4-Amino-2-(4-fluorophenyl)-1,2-dihydropyrimido[1,2-*a*]-benzimidazole-3-carbonitrile (**4e**). This compound was obtained according to above general procedure; ir (potassium bromide): 3424, 3314, 3206, 3052, 2890, 2190, 1675, 1632, 1598, 1252, 1066, 958, 810, 732 cm^{-1}; ^1H nmr: δ 8.60 (s, 1H, NH), 7.63 (d, 1H, J = 7.6 Hz, ArH), 7.35-7.31 (m, 2H, ArH), 7.24-7.18 (m, 3H, ArH), 7.12 (t, 1H, J = 7.6Hz, ArH), 7.01 (t, 1H, J = 7.6 Hz, ArH), 6.89 (s, 2H, NH_2), 5.25 (s, 1H, CH). *Anal* calcd. for $C_{17}H_{12}FN_5$: C, 66.88; H, 3.96; N, 22.94. Found: C, 66.69; H, 3.95; N, 22.86.

4-Amino-2-(2,4-dichlorophenyl)-1,2-dihydropyrimido[1,2-*a*]-benzimidazole-3-carbonitrile (4f). This compound was obtained according to above general procedure; ir (potassium bromide): 3422, 3310, 3208, 2902, 2198, 1675, 1562, 1281, 1044, 864, 740 cm^{-1}; ^1H nmr: δ 8.52 (s, 1H, NH), 7.68-7.66 (m, 2H, ArH), 7.48-7.46 (m, 1H, ArH), 7.40-7.38 (m, 1H, ArH), 7.25 (d, 1H, J = 8.0 Hz, ArH), 7.14 (t, 1H, J = 7.6 Hz, ArH), 7.03 (t, 1H, J = 7.6 Hz, ArH), 6.96 (s, 2H, NH_2), 5.64 (s, 1H, CH). *Anal* calcd. for $C_{17}H_{11}Cl_2N_5$: C, 57.32; H, 3.11; N, 19.66. Found: C, 57.52; H, 3.10; N, 19.59.

4-Amino-2-(4-methoxyphenyl)-1,2-dihydropyrimido[1,2-*a*]-benzimidazole-3-carbonitrile (4g). This compound was obtained according to above general procedure; ir (potassium bromide): 3423, 3323, 3216, 3157, 3006, 2907, 2187, 1679, 1637, 1599, 1424, 1249, 1032, 835, 739 cm^{-1}; ^1H nmr: δ 8.51 (s, 1H, NH), 7.63 (d, 1H, J = 8.0 Hz, ArH), 7.24-7.19 (m, 3H, ArH), 7.15-7.09 (m, 1H, ArH), 7.12 (t, 1H, J = 7.2 Hz, ArH), 7.00 (t, 1H, J = 7.6 Hz, ArH), 6.91 (d, 2H, J = 8.8 Hz, ArH), 6.80 (s, 2H, NH_2), 5.20 (s, 1H, CH), 3.72 (s, 3H, OCH_3). *Anal* calcd. for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07,. Found: C, 68.35; H, 4.75; N, 22.13

4-Amino-2-(3,4-dimethoxyphenyl)-1,2-dihydropyrimido-[1,2-*a*]benzimidazole-3-carbonitrile (4h). This compound was obtained according to above general procedure; ir (potassium bromide): 3431, 3323, 3217, 3064, 2932, 2837, 2189, 1682, 1600, 1469, 1400, 1263, 1026, 816, 740 cm^{-1}; ^1H nmr: δ 8.51 (s, 1H, NH), 7.63 (d, 1H, J = 8.0 Hz, ArH), 7.12 (d, 1H, J = 7.6 Hz, ArH), 7.11 (t, 1H, J = 7.6 Hz, ArH), 7.02-6.96 (m, 2H, ArH), 6.91 (d, 2H, J = 8.4 Hz, ArH), 6.84 (s, 2H, NH_2), 6.77 (d, 1H, J = 8.4 Hz, ArH), 5.19 (s, 1H, CH), 3.71 (s, 6H, $2OCH_3$). *Anal* calcd. for $C_{19}H_{17}N_5O_2$: C, 65.69; H, 4.93; N, 20.16. Found: C, 65.50; H, 4.92; N, 20.23.

4-Amino-2-(3,4,5-trimethoxyphenyl)-1,2-dihydropyrimido-[1,2-*a*]benzimidazole-3-carbonitrile (4i). This compound was

obtained according to above general procedure; ir (potassium bromide): 3447, 3331, 3225, 3161, 3001, 2937, 2838, 2186, 1686, 1593, 1459, 1325, 1005, 843, 725 cm^{-1}; ^1H nmr: δ 8.52 (s, 1H, NH), 7.63 (d, 1H, J = 8.0 Hz, ArH), 7.23 (d, 1H, J = 9.2 Hz, ArH), 7.12 (t, 1H, J = 7.2 Hz, ArH), 7.01 (t, 1H, J = 8.0 Hz, ArH), 6.87 (s, 2H, NH_2), 6.63 (s, 2H, ArH), 5.19 (s, 1H, CH), 3.70 (s, 6H, $2OCH_3$), 3.63 (s, 3H, OCH_3). *Anal* calcd. for $C_{20}H_{19}N_5O_3$: C, 63.65; H, 5.07; N, 18.56. Found: C, 63.84; H, 5.06; N, 18.46.

4-Amino-2-*p*-tolyl-1,2-dihydropyrimido[1,2-*a*]benzimidazole-3-carbonitrile (4j). This compound was obtained according to above general procedure; ir (potassium bromide): 3484, 3421, 3325, 3214, 3052, 2918, 2187, 1687, 1597, 1400, 1247, 1100, 819, 738 cm^{-1}; ^1H nmr: δ 8.53 (s, 1H, NH), 7.62 (d, 1H, J = 8.0 Hz, ArH), 7.23-7.09 (m, 6H, ArH), 7.00 (t, 1H, J = 7.2 Hz, ArH), 6.80 (s, 2H, NH_2), 5.15 (s, 1H, CH), 2.26 (s, 3H, CH_3). *Anal* calcd. for $C_{18}H_{15}N_5$: C, 71.74; H, 5.02; N, 23.24. Found: C, 71.93; H, 5.03; N, 23.17.

4-Amino-2-butyl-1,2-dihydropyrimido[1,2-*a*]benzimidazole-3-carbonitrile (4k). This compound was obtained according to above general procedure; ir (potassium bromide): 3390, 3270, 3164, 2954, 2929, 2190, 1688, 1598, 1398, 1144, 822, 732 cm^{-1}; ^1H nmr: δ 8.03 (s, 1H, NH), 7.59 (d, 1H, J = 7.6 Hz, ArH), 7.20 (d, 1H, J = 8.0 Hz, ArH), 7.09 (t, 1H, J = 7.2 Hz, ArH), 6.97 (t, 1H, J = 7.6 Hz, ArH), 6.67 (s, 2H, NH_2), 4.04 (s, 1H, CH), 1.54 (s, 2H, CH_2), 1.34-1.29 (m, 4H, $2CH_2$), 0.85 (s, 3H, CH_3). *Anal* calcd. for $C_{15}H_{17}N_5$: C, 67.39; H, 6.41; N, 26.20. Found: C, 67.20; H, 6.42; N, 26.21.

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