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Acid-catalyzed solvent-free synthesis of 2-arylbenzimidazoles under microwave irradiation

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Abstract

2-Arylbenzimidazoles have been synthesized from aromatic carboxylic acid and *o*-phenylenediamine under microwave irradiation (MW) and solvent-free conditions with catalytic amounts of acid in ambient pressure. This procedure constitutes a simple and practical green synthetic method for benzimidazoles and their structural analogs.

Keywords: Aromatic carboxylic acid; *o*-Phenylenediamine; 2-Arylbenzimidazoles; Acid-catalyzed; Solvent-free; Microwave

1. Introduction

The synthesis of substituted benzimidazoles has drew significant attention due to their biological activity and diverse medicinal uses such as antihistaminics, antiparasitics, antiulcers, antihypertensives, antivirals, antifungals and anticancers [1,2]. The widespread interest in substituted benzimidazole has prompted extensive exploration in their synthesis. Several methods have been developed for the synthesis of the 2-substituted benzimidazole and its derivatives [3–6]. These include the condensation of *o*-diamino aromatic compounds with carboxylic acids in the presence of strong acids or with the aldehydes in refluxing nitrobenzene [4], palladium-catalyzed reactions of haloaromatics and *o*-phenylenediamine under high carbon monoxide pressure [5], and the solid phase reactions [6]. Although some methods have been used in preparing 2-substituted benzimidazoles, they suffer from the drawbacks such as harsh reaction conditions (*i.e.*, the condensation of *o*-aryldiamines and carboxylic acids carried out by conventional thermal heating, heating under pressure in solvents, using a stoichiometric or excess amount of acid, and very high reaction temperatures), use of hazardous reagents, generation of toxic or environmentally harmful byproducts, low isolation yields, prolonged reaction time, and solid phase reaction resulted in the experimental difficulty. In view of the pharmaceutical application values of arylbenzimidazoles, it is worthwhile to search for milder and practical conditions that accelerate the cyclization rate of the benzimidazole moiety.

Microwave-assisted organic synthesis [7] (MAOS) has attracted considerable interest and is an important technique in green synthetic chemistry. It could help achieve high yields and clean reaction outcomes at short reaction time. Organic solvent-free reaction conditions eliminate the toxicity and flammability issues associated with common solvents. Together, solvent-free organic syntheses assisted by microwave irradiation (MW) have being regarded as environmentally benign methodologies. Some examples [8] in the preparation of substituted benzimidazoles using microwave-mediated protocols have been reported. However, these reactions are conducted in solvents such as nitrobenzene or dimethylsufoxide with additives such as transition metal complexes [8a–e]. Moreover, the condensation of aromatic carboxylic acid and *o*-phenylenediamine usually requires a large excess of strong acids, which could lead to the production of chemical wastes [8f]. No successful condensation using catalytic amounts of acids has been reported so far. In view of the power of MAOS, we envision that the condensation reaction may occur under the catalytic amount of HCl and the microwave irradiation (Scheme 1).

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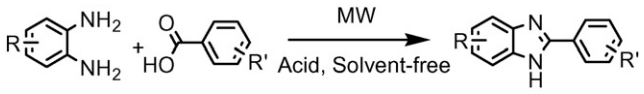


Scheme 1.

2. Results and discussion

In our initial attempts, microwave irradiation alone was found ineffective to condensate aromatic carboxylic acids with *o*-phenylenediamine in solvent-free conditions. The negative result suggests the necessity of catalysts for this reaction. For comparison, in the synthesis of azole hetercycles, additives such as bases to facilitate the acylation and acids to aid the dehydration are necessary for the high yield of azole hetercyles [9]. Along this line of thinking, Player and co-workers [10] speculated that the HCl released during the acylation of aminophenols with acyl chloride could catalyze the subsequent cyclization reaction in the synthesis of benzoxazoles. Similarly, Perry [11] reported that the small amount of HCl produced from $PdCl_2L_2$ did have a small positive effect in the cyclization reaction during the palladium-catalyzed synthesis of 2-arylbenzimidazoles from haloaromatics and *o*-phenylenediamine.

To verify the existence of such an auxiliary effect, we have investigated the effects of hydrochloric acid in the MW-assisted reaction of *o*-phenylenediamine and benzoic acid (Table 1). It was found that the condensation did occur at high yields under these conditions. In addition, the reaction proceeded smoothly even in the presence of air and moisture. As shown in Table 1, no product was formed in the absence of hydrochloric acid, and only a trace amount of product was observed using 1 mol% hydrochloric acid (Table 1, entries 7, 6). Remarkably, when 7–10 mol% hydrochloric acid were used, the product was obtained in 85–93% yields (Table 1, entries 3, 2). It was found that the amount of hydrochloric acid could be readily reduced to 10 mol% without compromising the high yields. However, when the catalyst loading was lowered to 3 mol%, incomplete conversions occurred despite longer reaction time (Table 1, entries 2–5).

Several acids have been tested to reveal their effects on the synthesis of 2-arylbenzimidazoles under solvent-free MW-assisted condition. It was found that strong acids such as HCl and H_3PO_4 gave the highest yields of the target compound (Table 2, entries 1, 2). Moderate yields were obtained when HNO_3, PPA, or H_2SO_4 were used instead (Table 2, entries 3–5). In comparison, weak acid such as HOAc gave a yield of 59% (Table 2, entry 6). Besides, it seems that protic acids are more effective than Lewis acids in catalyzing the reaction. For example, the reaction catalyzed by Lewis acid gave low yield (Table 2, entries 8–10). Sulfamic acid has emerged as a substitute for conventional acidic catalysts, whereas it is exceptional to our model experiment.

The ratio of aromatic carboxylic acid to *o*-phenyldiamine is an important factor for the yields of this condensation reaction. When the ratio was higher than 1.5:1, high yields of products were obtained (Table 3, entries 4 and 5). When the ratio was decreased to 1:1, the yield was lowered to 73% yield (Table 3, entry 1).

In order to characterize the scope of this method in preparing substituted benzimidazoles, we have examined the reactions of a variety of substituted aromatic carboxylic acids and substituted *o*-phenylenediamine under MW. As shown in Table 3, excellent yields of 2-arylbenzimidazoles were obtained from the aromatic carboxylic acids with electron-donating groups, such as methyl, methoxy and hydroxyl group (Table 4, entries 2–5, 11 and 12). The steric hampered 4′-methylbiphenyl-2-carboxylic acid was

Table 1
Effect of hydrochloric acid and its amount on the condensation reaction[a]

Entry	Amount of catalyst (mol%)	Reaction time (min)	Yield (%)[b]
1	15	10	93
2	10	10	93
3	7	10	85
4	5	20	78
5	3	20	17
6	1	20	Trace
7	0	30	0

[a] The mixture of the *o*-phenylenediamine (8 mmol) and benzoic acid (12 mmol) with hydrochloric acid (8N) was irradiated under microwave using a domestic microwave oven at 600 W.
[b] Isolated yield.

Table 2
Effect of various acid on the condensation reaction[a]

Entry	Acid[b]	Reaction time (min)	Yield (%)[c]
1	HCl	10	93
2	H_3PO_4	10	92
3	HNO_3	10	84
4	PPA	10	77
5	H_2SO_4	10	73
6	HOAc	10	59
7	NH_2SO_3H	15	46
8	$FeCl_3$	10	32
9	$ZnCl_2$	10	30
10	$AlCl_3$	10	26

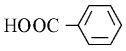
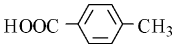
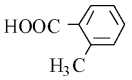
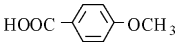
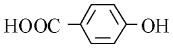
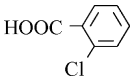
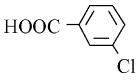
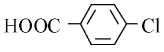
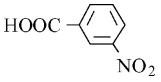
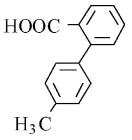
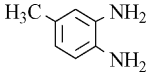
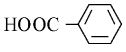
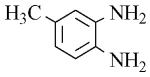
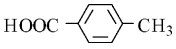
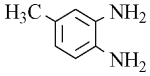
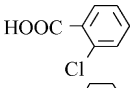
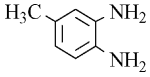
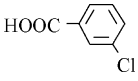
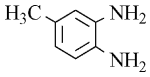
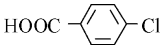
[a] The mixture of the *o*-phenylenediamine (8 mmol) and benzoic acid (12 mmol) was irradiated under microwave using a domestic microwave oven at 600 W.
[b] 10% mol of various acid (8N) was used.
[c] Isolated yield.

Table 3
Effect of the ratio of *o*-phenylenediamine-carboxylic acid on the condensation reaction[a]

Entry	Diamine: acid[b]	Reaction time (min)	Yield (%)[c]
1	1	10	73
2	1.1	10	76
3	1.2	10	82
4	1.5	10	93
5	2	10	93

[a] The mixture of the *o*-phenylenediamine (8 mmol) and benzoic acid (12 mmol) with 10% mol of hydrochloric acid (8N) was irradiated under microwave using a domestic microwave oven at 600 W under atmospheric pressure.
[b] The mol/mol of *o*-phenylenediamine to carboxylic acid.
[c] Isolated yield.

Table 4
Condensation of various carboxylic acids with *o*-phenylenediamine under microwave irradition[a]

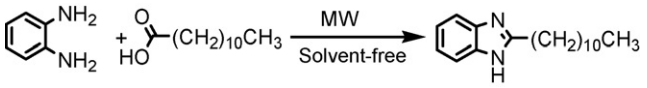
Entry	*o*-Phenylenediamine	Carboxylic acid	Reaction time (min)	Yield (%)[b]
1			10	93
2			10	96
3			10	87
4			10	88
5			10	78
6			10	81
7			10	72
8			10	77
9			10	73
10			20	62
11			10	95
12			10	93
13			10	83
14			10	76
15			10	78

[a] The mixture of *o*-phenylenediamine (8 mmol) and carboxylic acids (12 mmol) with 10% mol of hydrochloric acid (8N) was irradiated under microwave using a domestic microwave oven at 600 W.
[b] Isolated yield of the 2-arylbenzimidazoles, confirmed by ^{1}H NMR.

less reactive than others, as the benzimidazole was generated at a yield of 62% under otherwise the same condition (Table 4, entry 10). Moderate yields were observed for the carboxylic acid with electron-withdrawing substitutents such as chloro and nitro groups (Table 4, entries 6–9 and 13–15). The latter result is enouraging, due to the oxidation effect of the nitro group at elevated temperature the presence of nitro group-containing reactants sometimes leads to the carbonization of the reaction mixture upon thermal heating. In the current study, MW heating was found to suppress the occurrence of product oxidation, and the yield of 2-arylbenzimidazoles from 3-nitrobenzoic acid is a reasonable 73%.

In general, the reactions [12] proceeded efficiently in the presence of catalytic amounts of hydrochloric acid and were complete within 10 min under solvent-free and MW-assistaed conditions. In all cases, the products were clean as indicated by TLC, and the benzimidazole products were conveniently obtained by silica gel chromatography. In contrast, the conventional reactions require excess amounts of acid to serve as solvent under pressure, and they take 10–20 h only to afford yields comparable with those reported in this paper.

It was found that aliphatic carboxylic acid also reacted with *o*-phenylenediamine to generate the corresponding 2-alkylbenzimidazoles under the similar reaction condition.



Scheme 2.

Table 5
Condensation of various carboxylic acids with 2-aminophenol assisted by microwave irradiation[a]

Entry	Carboxylic acid	Reaction time (min)	Yield (%)[b]
1	HOOC–	17	76
2	HOOC–CH_3	17	77
3	HOOC–OCH_3	17	80

[a] The mixture of 2-aminophenol (8 mmol) and carboxylic acids (12 mmol) with 10% molar hydrochloric acid (8N) was irradiated under microwave using a domestic microwave oven at 600 W.
[b] Isolated yield after silica gel chromatography, confirmed by ^{1}H NMR.

Interestingly, this MW-assisted, solvent-free reaction requires no externally added acid catalyst, and gave a yield as high as 93% (Scheme 2). In an attempt to explore the generality of this method in preparing the structural analogs of benzimidazoles, we found that the coupling of 2-aminophenol with aromatic carboxylic acids under similar conditions proceeded smoothly to give the desired 2-arylbenzoxazoles in good yields (Table 5, entries 1–3).

3. Conclusion

In summary, we have developed a fast and convenient method to synthesize 2-arylbenzimidazoles with high yields from *o*-phenylenediamine and aromatic carboxylic acids. These reactions were conducted in the presence of catalytic amount hydrochloric acid, without using solvent, and assisted by MW. We also showed that similar reaction conditions are suitable for the syntheses of alkylbenzimidazoles from aliphatic carboxylic acids and 2-arylbenzoxazoles from 2-aminophenol, respectively. The salient features of this method include the simple reaction set-ups, mild reaction conditions, and short reaction time. These advantages should render the synthesis of benzimidazoles and the related compounds more efficient and environmental friendly.

Acknowledgments

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[12] Typical Procedure for the Synthesis of 2-substituted benzimidazoles: *o*-Phenylenediamine (8 mmol), carboxylic acid (12 mmol) and hydrochloric acid (8 N, 0.8 mmol) were mixed thoroughly in a round–bottom flask (50 ml) that is connected with a condenser. The flask was placed in a domestic microwave oven (Whirlpool, Model MCL-Tr, 850 W, 2450 MHz) and heated under microwave-assisted dielectric heating (micromode, irradiated at 600 W) in 192 °C (measured by IR Thermometer) for an appropriate total irradiation time (monitored by TCL). All microwave experiments were conducted at atmospheric pressure. The temperature was measured via IR Thermometer (Minolta, HT21) in the reaction vessel. The temperature was controlled by modulation of power. After cooling, the reaction mixture was added with water, and then neutralized with 1N NaOH, the precipitated was filtered and dried, then recrystallized from ethanol/water to give the corresponding 2-substituted benzimidazoles. **2-(4′-Methylbiphenyl)benzimidazol**e is a new compound, its structure was characterized by its spectral data and elemental analysis: m.p. 260–261 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 2.24 (s, 3 H), 7.04–7.09 (dd, J = 7.4 Hz, J = 1.8 Hz, 4H), 7.12–7.14 (m, 2H), 7.33–7.35 (t, J = 7.4 Hz, 1H), 7.49–7.51 (t, J = 7.2 Hz, 2H), 7.57–7.60 (m, 2H), 7.68–7.69 (d, J = 8.0 Hz, 1H), 12.08 (br s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ = 21.1, 119.3, 121.6, 122.5, 127.6, 129.1, 129.2, 130.3, 130.4, 130.6, 130.8, 131.6, 135.0, 136.7, 137.7, 141.3, 143.9; MS (EI) m/z 285.1 (MH^+). Anal. Calcd. for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.50; H, 5.63; N, 9.82.