

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

Rui Wang^a, Xiao-xia Lu^{b,*}, Xiao-qi Yu^a,
Lin Shi^b, Yong Sun^a

^a Department of Chemistry, Key Laboratory of Green Chemistry & Technology, Sichuan University, Chengdu 610064, P.R. China

^b Chengdu Institute of Biology, Chinese Academic of Sciences, Chengdu 610041, P.R. China

Received 3 March 2006; accepted 19 April 2006

Available online 18 November 2006

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.

© 2006 Elsevier B.V. All rights reserved.

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

1. Introduction

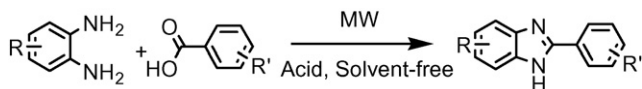
The synthesis of substituted benzimidazoles has drew significant attention due to their biological activity and diverse medicinal uses such as antihistaminics, antiparasitics, antiulcers, antihypertensives, antivirals, antifungals and anticancers [1,2]. The widespread interest in substituted benzimidazole 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 been 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 dimethylsulfoxide 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).

* Corresponding author. Tel.: +86 28 85253276

E-mail address: xlua71@yahoo.com.cn (X.-x. Lu).



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 heterocycles, additives such as bases to facilitate the acylation and acids to aid the dehydration are necessary for the high yield of azole heterocycles [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 PdCl₂L₂ 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

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 ₃ PO ₄	10	92
3	HNO ₃	10	84
4	PPA	10	77
5	H ₂ SO ₄	10	73
6	HOAc	10	59
7	NH ₂ SO ₃ H	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.

H₃PO₄ gave the highest yields of the target compound (Table 2, entries 1, 2). Moderate yields were obtained when HNO₃, PPA, or H₂SO₄ 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 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.

Download English Version:

<https://daneshyari.com/en/article/67996>

Download Persian Version:

<https://daneshyari.com/article/67996>

[Daneshyari.com](https://daneshyari.com)