

Article

Highly efficient synthesis of benzimidazoles using microwave irradiation.

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Abstract: A microwave assisted method for synthesis of 1,2-disubstituted benzimidazoles has been developed. The combination of molar ratio *N*-phenyl-*o*-phenylenediamine:benzaldehyde (1:1) using microwave irradiation and only 1% mol of Er(OTf)₃ provide an efficient, environmental and mild access to a diversity of benzimidazoles under solvent-free conditions.

Keywords: microwave; green chemistry; benzimidazoles

1. Introduction

The use of toxic solvents in the pharmaceutical industry is a serious problem for the environment and human health, but in the last years, Green Chemistry principles influenced the activities drug industries introducing less use of classic organic solvents [1-3], cuts in waste production with the use the recyclable reagents [4-8] and environmental organic synthetic methods.

Various research studies have been conducted on the use of “green” solvents [9-12], principally bio-solvents [13-17], ionic liquids [18-20], deep eutectic solvents [21-26], supercritical fluids [27,28], or water [29-37]. Certainly, adopting methods experimental tests based on solvent-free or solid-state reaction conditions reduces pollution. These reactions may be carried out using the reactants alone. Often the same reactions involve use of solid supports (clays, zeolites, silica, alumina or other matrices) making it easier the experimental and work-up procedures improving yield, increasing the reaction rate and lowering considerably environmental impact [38-40].

The reactions in solvent-free conditions under ultrasonic [41] or microwave [42] irradiation play a very important role in eco-sustainable extraction [43-45] and synthesis [46-53] because they greatly prevent waste and often only irradiation is useful for activating the organic reaction.

Due to their properties and applications, benzimidazoles are a class of heterocyclic compounds of great interest in the pharmaceutical chemistry area. Benzimidazole ring constitutes the basic structure of important and different pharmaceutical agents [54-58] as the vitamin B₁₂ [59]. For this reason, the synthesis of benzimidazoles derivatives has had considerable interest in the development of organic synthetic processes applicable on an industrial scale and with a low environmental impact.

Recent research on the use of eco-sustainable solvents in organic chemistry for the synthesis of benzimidazoles [60-62] has had great prominence in the scientific community as well as the use of Lewis acid catalysis exploitation homogeneous catalysts [63-66] in mild reaction conditions. At the same time, experimental reactions using solid supports in conventional solvents [67-70], in green solvents [71, 72] or under solvent-free conditions [73-76] performed and the use of heterogeneous catalyst under solvent-free conditions [77] has been particularly important for the eco-sustainable synthesis of benzimidazoles.

However, the synthetic procedure for the synthesis of 1,2-disubstituted benzimidazole derivatives requires the use of MK10 20% wt with a selectivity that is not always high. Therefore, the synthetic method has often involved the use of purification systems to obtain the desired 1,2-substituted benzimidazole derivative.

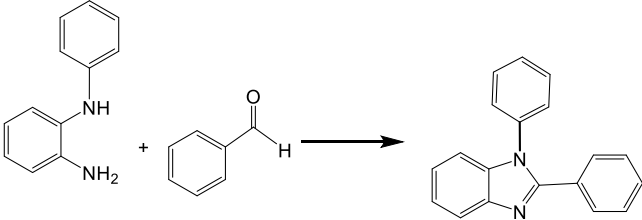
Considering our experience in Lewis acid catalysis and testing the catalytic activity of Er (III) in reactions under microwave irradiation [78-82] and in the synthesis of benzimidazole [25, 83] and benzodiazepine [84,85] derivatives, we report the development of new, ecofriendly and mild method MW- assisted for the synthesis of a variety of substituted benzimidazoles. The synthetic method does not require the use of solvents but require the use of only 1% Er(OTf)₃ as catalyst for the formation of benzimidazole derivatives.

2. Results

In our initial experiment, we choose *N*-phenyl-*o*-phenylenediamine (1 mmol) and benzaldehyde (1 mmol) starting material in the different green solvent at different temperature to obtain selectively 1,2-disubstituted benzimidazole derivative **1a** (Table 1). Initially, we tested the effect of temperature on the model reaction performing the reaction (Table 1, entry 1) using ethyl lactate as solvent. The reaction mixture, stirred at room temperature for 2 h, is executed monitoring reaction by thin layer chromatography (TLC) and gas chromatography/mass spectrometry (GC/MS) analysis.

The temperature effects showed that increasing the reaction temperature to 100 °C yields are higher but insufficient (Table 1, entry 3).

At room temperature in waters as solvent, the GC/MS analysis showed the low conversion of the reagents within 2 hours even when increasing the temperature at 60° (Table 1, entries 4 and 5). The GC-MS analysis showed the presence of the 1,2-disubstituted benzimidazole derivative with higher yields (59.6 % yields) at 60° C in only 120 minutes (Entry 6 in Table 1) and at a higher temperature in the same reaction time (100°C, 120 min.) (Table 1, entry 7) the reaction yield increased considerably (89.7 %). When the mixture reaction subjected to microwave irradiation we obtained a good yield in only ten minutes at 60° C (Table 1, entry 8). Interesting was the result obtained when the reaction was carried out in (Table 1, entry 9). At this point, exploiting the activity of microwave radiation for activating the organic reactions in solvent free condition, the good conversion of *N*-phenyl-*o*-phenylenediamine was observed obtaining the reaction product at 89.6 % of yield after only 15 minutes (Table 1, entry 10). The model reaction showed the complete conversion of *N*-phenyl-*o*-phenylenediamine when the same reaction was performed in solvent free condition at 60° C in only 5 minutes adding only 1% Er(OTf)₃ at mixture reaction (Table 1, entry 10).

Table 1. Optimization of the reaction conditions.^a


c	Solvent	Temp (°C)	Time (min)	Yield (%) ^b
1	Ethyl lactate	rt	120	0
2	Ethyl lactate	60	120	3.9
3	Ethyl lactate	100	120	15.3
4	water	rt	120	10.2
5	water	60	60	20.9
6	water	60	120	59.6
7	water	100	120	89.6
8 ^c	water	60	10	71.9
9	-	60	60	61.4
10 ^c	-	60	5	89.6
11 ^{c,d}	-	60	5	99.9

^a General reaction conditions: *N*-phenyl-*o*-phenylenediamine (1 mmol) and benzaldehyde (1 mmol) were stirred for 5-120 min at different temperatures in appropriate solvent. ^bPercent yield calculated from GC/MS data of the corresponding disubstituted benzimidazole derivative. ^cReaction mixture under MW irradiation. ^d Er(OTf)₃ (1% mol).

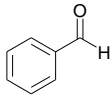
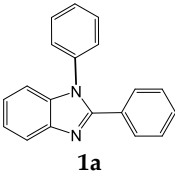
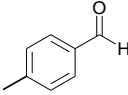
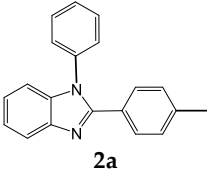
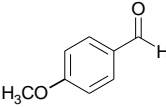
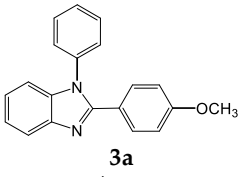
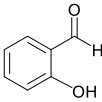
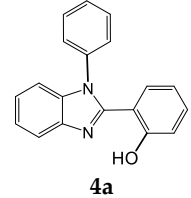
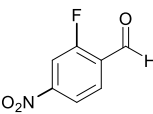
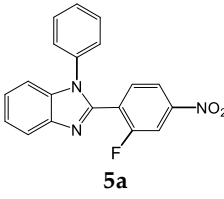
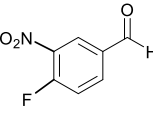
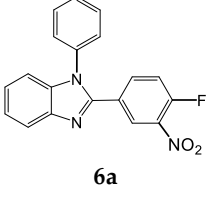
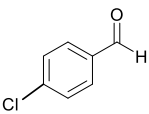
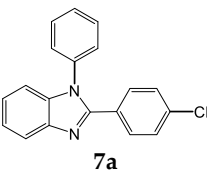
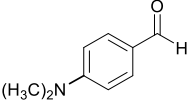
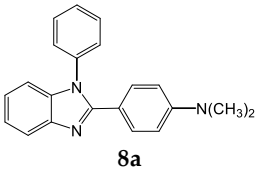
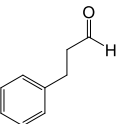
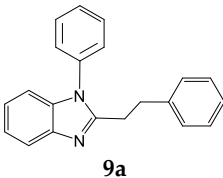
The only reagents used to obtain respective product crude in faster reaction times are been the aldehyde and the *N*-phenyl-*o*-phenylenediamine. MW-activation for the benzimidazole formation reduces the reaction times (from 60 min to 5 min) and enhances the yield as well (from 61.4% to 99.9%).

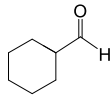
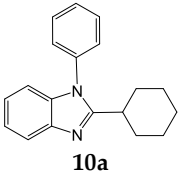
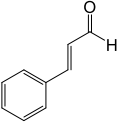
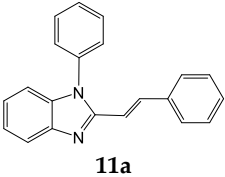
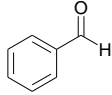
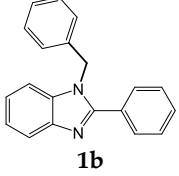
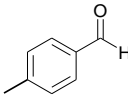
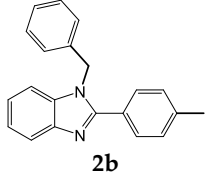
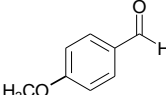
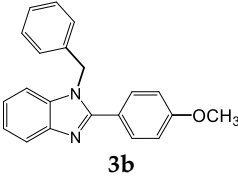
At this point, the experimental procedure was applied to different aldehydes to obtain the related disubstituted benzimidazoles, and quantitative yields superior to 96% were obtained in all cases (Table 2).

The high-yield reaction was reported using different substituted benzaldehydes such as *p*-methyl, *p*-methoxy and *o*-hydroxy benzaldehyde (entries 2, 3 and 4, Table 2). The reactions performed with *p*-chloro, *p*-fluoro *p*-nitro benzaldehyde, aldehydes containing electron withdrawing groups, (entries 5, 6 and 7, Table 2) afford the corresponding disubstituted benzimidazoles (**4a-7a**) in good yields (detected by GC/MS) but in the longer reaction times (after 15 minutes).

As shown in Table 2, this new method works maintained high catalytic activity on various substituted benzaldehydes, alkyl aldehydes and cinnamaldehydes (entries 8,9 and 10). The performed reactions with *N*-benzyl *o*-phenylenediamines as *N*-alkyl-*o*-phenylenediamines maintained the same reaction yield in the same condition e in the same reaction times (Table 2, entries 12, 13 and 14)

Table 2. Synthesis of 1,2-disubstituted benzimidazoles^a

Entry	Aldehyde	Product	Time (min)	Yield (%) ^b
1		 1a	5	99.9
2		 2a	5	98.6
3		 3a	7	99.6
4		 4a	10	96.3
5		 5a	15	96
6		 6a	15	97
7		 7a	10	97
8		 8a	15	91.1
9		 9a	5	98.2

10		 10a	5	98.8
11		 11a	12	85.8
12 ^c		 1b	5	99.9
13 ^c		 2b	5	98.9
14 ^c		 3b	5	99.8

^a General reaction conditions: The mixture reaction (1 mmol of *N*-phenyl-*o*-phenylenediamine, 1 mmol of aldehyde and 1% mmol of Er(OTf)₃) conducted in a Syntos 3000 microwave oven (Anton-Paar) at 60°C for 5-10 min. The reaction mixture giving the corresponding products **1a-8a**. ^b Percent yield calculated from GC/MS data. ^c The mixture reaction conducted in the same reaction conditions using the *N*-benzyl-*o*-phenylenediamine as *N*-substituted-*o*-phenylenediamine.

The use of the irradiation microwave has made the reaction process even more green than the previously methodologies, for faster reaction times and for greater selectivity of product formation. In the development of a green synthetic procedure, the isolation of the product is additional significant point. In our method, the benzimidazole derivatives could easily be isolated by simple addition of water and extraction with ethyl acetate, a green solvent.

Then, we also found it necessary to demonstrate the potential industrial applicability of this eco-friendly procedure, the preliminary reaction to give **1a** was carried out in a large scale (20 mmol of *N*-phenyl-*o*-phenylenediamine and 20 mmol of benzaldehyde). The reaction was completed in 25 min with excellent yield (93%) after simple water addition and extraction with ethyl acetate.

In conclusion, we reported a green and simple procedure for the synthesis of benzimidazoles. All reactions performed in short reaction times (5-10minutes) and with reaction yields of 86 to 99% (Table 2).

Unlike the methods reaction reported in the literature, the procedure described does not require for the use of solvents but only microwave irradiation to perform the

complete reaction process. The proposed method reduces reaction time and energy consumption, developing the process industrially appropriate

3. Materials and Methods

3.1. General Methods

All reactions were monitored by GC-MS Shimadzu workstation. It is constituted by a GC 2010 (equipped with a 30 m-QUADREX 007-5MS capillary column, operating in the “split” mode, 1 mL min⁻¹ flow of He as carrier gas).

¹H-NMR and ¹³C-NMR spectra were recorded at 300 MHz and at 75 MHz respectively, using a Bruker WM 300 system. The samples solubilized in CDCl₃ using tetramethylsilane (TMS) as reference (δ 0.00). Chemical shifts are given in parts per million (ppm) and coupling constants (J) are given in hertz. For ¹³C-NMR the chemical shifts are relative to CDCl₃ (δ 77.0).

Synthos 3000 instrument from Anton Paar, equipped with a 4 × 24MG5 Rotor, used for the MW-assisted reactions. An external IR sensor monitors the temperature at the base of each reaction vessel.

3.2 General Procedure for the Synthesis of 1-phenyl-2-Aryl(alkyl) Benzimidazoles 1a-11a.

The aryl or alkyl aldehyde (1 mmol) was added to the *N*-phenyl-*o*-phenyldiammine (1 mmol) and Er(OTf)₃ (1% mol). The obtained mixture reaction was reacted for 5 min under microwave assisted, at a temperature of 60 °C (IR Limit). After completion conversion of *N*-phenyl-*o*-phenyldiammine, the Er(OTf)₃ was separated from the reaction mixture adding water and extracting the organic product with ethyl acetate (4x3 mL). The products were isolated after organic phases dried over Na₂SO₄, followed by evaporation under reduced pressure. Spectral data were in accordance with the literature [86]

3.3 General Procedure for the Synthesis of 1- benzyl-2-Aryl-Benzimidazoles 1b-3-b.

The benzaldehyde or *p*-sostituted-benzaldehyde (1 mmol) was added to the *N*-benzyl-*o*-phenyldiammine (1 mmol) and Er(OTf)₃ (1% mmol). The obtained mixture reaction was reacted in the same reaction conditions previously reported (MW irradiation for 5 min). After completion conversion of *N*-phenyl-*o*-phenyldiammine, the Er(OTf)₃ was separated from the reaction mixture adding water and extracting the organic product with ethyl acetate (4x3 mL). The products were isolated after organic phases dried over Na₂SO₄, followed by evaporation under reduced pressure. Spectral data were in accordance with the literature [87].

4. Conclusions

In summary, the current research proved a rapid, cheap, clean and environmentally sustainable method microwave assisted for the synthesis of 1,2-bisubstituted benzimidazoles. The procedure does not require the use of solvent and the simple product recovery.

The use of the Lewis catalyst Er(OTf)₃ (1% mmol) provides a synthetic procedure which considerably reduces reaction times and waste reaction, further promoting the green chemistry principles and industrial application.

Supplementary Materials: The following are available online at www.mdpi.com/link.

Author Contributions: M.N. conceived and designed the experiments; S.B. performed the experiments; N. H. C. and M.O. analyzed the data; M. N. and A.P. wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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