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NOTE

Microwave-assisted Synthesis of Some Benzimidazole Derivatives: A Case for a Comparative Study

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Benzimidazole derivatives (**3a–k**) were synthesized in high yield (80–95%) using a microwave assisted cyclocondensation reaction of *o*-phenylenediamine and a carboxylic acid under acidic medium. Products were recrystallized from a mixture of ethanol and water. Synthesis of benzimidazole derivatives under microwave irradiation is found much easier and faster than conventional heating method.

Key Words: *o*-Phenylenediamine, Benzimidazole, Irradiation, Microwave.

Benzimidazoles are very interesting heterocyclic compounds with having different biological properties. Some of them are very important due to having chemotherapeutic[1–6] and biological effects[7–9]. Microwave irradiation is a non-conventional energy source, which has been of special interest in organic chemistry in recent years[10–13]. Some of interesting features of this method are the rapid reaction rates, simplicity and cleaner reaction conditions[13–15].

In order to synthesis of some benzimidazoles derivatives in a clean and faster method, it was decided to investigate the influence of microwave irradiation on a heterocyclization of *o*-phenylendiamine, carboxylic acid in acidic medium.

EXPERIMENTAL

All chemicals including *o*-phenylenediamine, carboxylic acids were of reagent grade quality and used without further purification. ^{1}H NMR spectra were recorded on a Brucker 500 MHz spectrometer. IR spectra were performed on a Galaxy FT-IR 500 spectrophotometer. Reaction proceed was routinely monitored by thin layer chromatography (TLC) on silica gel plates. Reactions were performed in a Samsung microwave oven with a 230V–50Hz power source, 900W output and 2450 MHz operating frequency. All products were characterized by comparison of their spectra (IR, ^{1}H NMR) with those of authentic samples, which were prepared under reflux.

General procedure: *o*-phenylenediamine (1.0 mmol) was ground in a pestle and mortar with an appropriate carboxylic acid (1.0 mmol). The mixture was placed in a 25 mL glass beaker and two drops of hydrochloric acid (4 M) added. This

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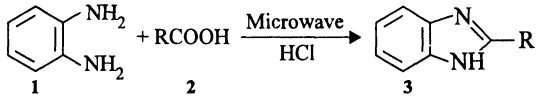
beaker was laid into the microwave oven and subjected to microwave irradiation at 50% power level for 1.5 to 4 min depending on used carboxylic acid. The crude products were recrystallized from a mixture of ethanol and water (50 : 50) to give compounds **3a–k.**

RESULTS AND DISCUSSION

Benzimidazoles **3a–k** were prepared by heterocyclization of *o*-phenylendiamine **1** and appropriate carboxylic acid **2** under acidic medium and microwave irradiation **(Scheme-1).**



1 2 3

(3a) R = Methyl; **(3b)** R = [4-(1H-1,3-benzymidazole-2-yl) butyl; **(3c)** R = Propyl; **(3d)** R = Ethyl; **(3e)** R = 1-Hydroxyethyl; **(3f)** R = Heptyl; **(3g)** R = [2-(1H-1,3-benzimidazole-2-yl)ethyl]; **(3h)** R = Chloromethyl; **(3i)** R = 2-Mercaptomethyl; **(3j)** R = 2-Phenylethyl; **(3k)** R = 4-nitrophenyl.

Scheme-1

In all experiments, molar ratio 1 : 1 of two starting materials, **1, 2** and two drops of hydrochloric acid (4M) were mixed and subjected to microwave irradiation for 1.5 to 4 min. The method is very easy and can be used for synthesis of different benzimidazoles **3a–k** depending on R groups or acids (Table-1). In some cases, acids containing two acidic functional groups like adipic and succinic acids were used, both functional groups react with *o*-phenylendiamine to produce entries **3b** and **3g,** which have in turn two benzimidazole rings. Yields of these one-pot reactions following recrystallization from ethanol were of the order of 80–95% (Table-1), which is most favourable as compared with conventional heating method (Table-1).

TABLE-1
COMPARISON OF TIME AND YIELDS ON THE FORMATION OF SOME BENZIMIDAZOLE DERIVATIVES USING MICROWAVE IRRADIATION AND CONVENTIONAL HEATING

Entry	Carboxylic acid	Microwave irradiation		Conventional heating		
		t/min	Yield %	t/min	Yield %	t_c/t_{mv}
3a	Acetic acid	1.5	90	240	60	160
3b	Adipic acid	2.0	85	270	70	135
3c	Butyric acid	2.0	95	240	70	120
3d	Propanoic acid	1.5	95	240	75	160
3e	Lactic acid	2.5	92	240	90	96
3f	Octic acid	3.0	95	240	40	80
3g	Succinic acid	2.5	85	240	70	96
3h	Chloroacetic acid	4.0	90	240	85	60
3i	Thioglycolic acid	1.5	95	240	90	160
3j	Cinnamic acid	4.0	80	240	40	60
3k	*p*-Nitrobenzoic acid	4.0	95	240	80	60

Table-1 compares the synthetic conditions of benzimidazole derivatives under microwave irradiation and conventional heating. Synthesis of benzimidazoles from carboxylic acids, especially aryl carboxylic acid and *o*-phenylinediamine need vigorous reaction conditions. Several authors have reported such different vigorous conditions for synthesis of different benzimidazoles[16]. However, microwave irradiations enter these reactions easily so that synthesis of **3a–k** under microwave irradiation is 60–160 times faster than conventional heating methods. This ratio between the reaction times (t_c/t_{mv}) using conventional heating and microwave irradiation reflects the microwave heating effect.

In conclusion, the rapid heating induced by microwave irradiation not only avoids the force conditions and the decomposition of the reagents but also results in formation of clean product under mild conditions, thus increasing the yield. As a result synthesis of benzimidazoles **3a–k** under microwave irradiation are more convenient and faster than conventional heating.

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