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ORIGINAL ARTICLE

Amberlite IR-120 catalyzed, microwave-assisted rapid synthesis of 2-aryl-benzimidazoles

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Microwave irradiation

Abstract An expeditious synthesis of 2-aryl-benzimidazoles by the condensation of *o*-phenylenediamine with various araldehydes is described. This greener protocol is catalyzed by Amberlite IR-120, and proceeds efficiently in the absence of any organic solvent under microwave irradiation within 3–5 min.

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1. Introduction

Microwave technology has become very important in organic synthesis, and there are very few areas of synthetic organic chemistry, which have not been covered by this technology. It has been noted that microwave chemistry can provide access to synthetic transformations, which may otherwise be time consuming or low yielding using conventional heating (De La Hoz et al., 2004).

Benzimidazoles are key building blocks of a number of natural products, pharmaceuticals and synthetic intermediates. The benzimidazole ring is an important pharmacophore in modern drug discovery (Tebbe et al., 1997). Benzimidazoles exhibit significant activity against several viruses, such as influenza (Tamm, 1957), herpes (HSV-1) (Migawa et al., 1998), HIV (Porcari et al., 1998; Roth et al., 1997), and human cytomegalovirus (HCMV) (Tebbe et al., 1997); have also been used as potential antimicrobial (Forseca et al., 2001) anti-tumor agents (Denny et al., 1990) and for the treatment of interstitial cystitis (Iyenger et al., 1997). The discovery of novel synthetic routes towards benzimidazoles is an area of current interest, and the methods developed for the preparation of these heterocycles include: condensation of acid chlorides (Heuser et al., 2005) carboxylic acids, (Bai et al., 2001), nitriles (Nadaf et al., 2004), orthoesters (Hein et al., 1957), esters (Terashima and Ishii, 1982), amides (Jenkins et al., 1961) or aldehydes (Chakraborti et al., 2004) with *o*-phenylenediamine. Because of the availability of a vast number of aldehydes, the condensation of *o*-phenylenediamine with aldehydes has been studied in the presence of various catalysts including CAN (Rajesh and Joshi, 2007), *p*-TsOH (Han et al., 2002) Ammonium metavanadate (Ganesh et al., 2009a,b), Heteropolyacids (Majid et

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al., 2008) and $\text{Cu}_3/2\text{PMO}_{12}\text{O}_{40}/\text{SiO}_2$ (Razieh and Hamid, 2009). However, the reported procedures suffer from one or the other disadvantages, such as long reaction duration, low yield of the products, use of excess amount of reagents and tedious workup procedures. In addition, some of the catalysts and reagents are expensive and toxic in nature. Thus, there is still a need to search for better catalysts and a procedure with operational simplicity.

It has been reported that condensation of *o*-phenylenediamine and two equivalents of aldehyde in the presence of catalysts, such as $\text{SiO}_2/\text{ZnCl}_2$ (Raquel et al., 2009), montmorillonite K-10 (Perumal et al., 2004), $\text{M}(\text{HSO}_4)_n$ (Niknam et al., 2008), and amberlite IR-120 (Saikat and Dilip, 2009) gives 1-arylmethyl-2-aryl-benzimidazoles (**4**, Scheme 1). The amberlite IR-120 catalyzed reaction is carried out in the presence of a solvent and the reaction takes a long time for completion (6.5 h). Also, there are procedures wherein the formation of both the mono-substituted benzimidazoles (**3**) and di-substituted benzimidazoles (**4**) is reported (Ravi et al., 2007; Ganesh et al., 2009a,b).

In continuation of our work on the development of simple and environmentally friendly experimental procedures using readily available reagents and catalysts for the synthesis of biologically active molecules, such as 3,4-dihydropyrimidin-2(1H)-ones/-thiones (Pasha and Jayashankara, 2005, 2006), nitriles (Pasha and Aatika, 2010), 5-arylmethylidene-2-phenyloxazol-4-ones (azalactones) (Madhusudana and Pasha 2010), bis (indolyl) methanes (Pasha et al., 2008) 1,2,4,5-tetra-aryl-imidazoles (Aatika and Pasha, 2011), α -iodoacetates (Myint and Pasha, 2004), and 2-aminobenzochromene (Pasha and Jayashankara, 2007), under solvent-free microwave condition. We, in this article, are reporting the use of a heterogeneous catalyst amberlite IR-120 for the exclusive synthesis of mono-substituted benzimidazoles (**3**) from *o*-phenylenediamine and one equivalent of an araldehyde under solvent-free microwave irradiation.

2. Results and discussion

The reaction between one equivalent of *o*-phenylenediamine and one equivalent of an araldehyde in the presence of catalytic amounts of amberlite IR-120 under solvent-free microwave irradiation is fast, clean and high-yielding and all the reactions go to completion in 3–5 min. The highlighting feature of this protocol is: (i) the method is highly efficient and selective; (ii) the catalyst is recyclable; (iii) gives excellent yield of the products; (iv) all the reactions go to completion within 5 min when compared with other reported methods.

Comparison of the results of the present method with the literature methods for the synthesis of 2-aryl-benzimidazoles (**3**) indicates that the reported reactions take a prolonged period varying from 10 min to 7 h giving products in the yields ranging from 60% to 98%. Our method is advantageous as the reactions go to completion within 3–5 min and give excellent yield of the products (95–98%).

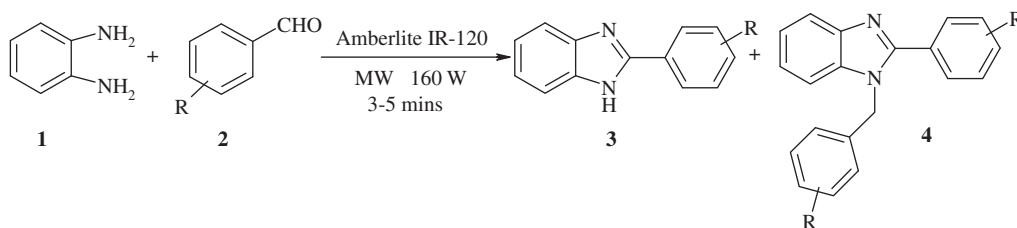
For optimising the reaction, it was examined under three different conditions: (i) thermal solvent-free condition; (ii) reflux in acetonitrile and (iii) under solvent-free microwave irradiation. Firstly, *o*-phenylenediamine (1 mmol) and benzaldehyde (1 mmol) were taken, and 0.20 g of amberlite IR-120 was added and the mixture was heated for 10 min or refluxed for 30 min in acetonitrile to get 50% of product **3a** [the progress of the reaction was monitored on TLC], continuation of the reaction did not improve the yield of the product. When the same reaction was carried out under the influence of microwave irradiation in the absence of solvent, the reaction proceeded effectively affording the product in 95% yield in 5 min. After optimising these conditions using benzaldehyde as a model aldehyde, the reactions were performed with various other araldehydes, and it was noticed that the reaction proceeds well with all types of araldehydes and the results of this study are presented in Table 1.

3. Experimental

All the reactions were carried out using a conventional (unmodified) household microwave oven (LG, 230 V, ~50 Hz). Reactions were monitored on TLC by comparison with the samples prepared by known procedures. The ^1H NMR spectra of the products were recorded on a Bruker AMX (400 MHz) spectrophotometer. LC-Mass spectra were recorded on an Agilent Technologies 1200 series instrument. Yields refer to the isolated yields of the products.

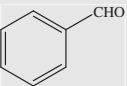
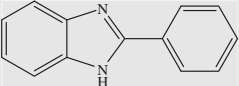
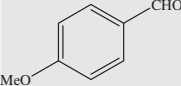
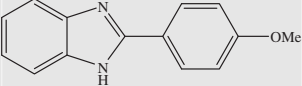
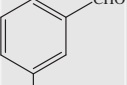
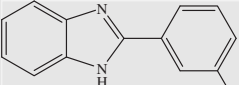
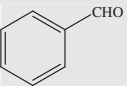
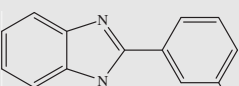
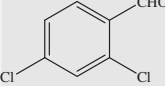
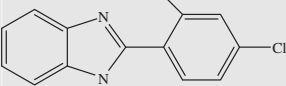
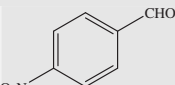
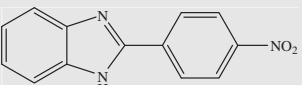
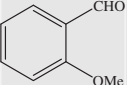
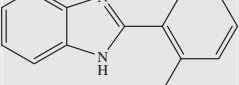
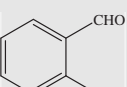
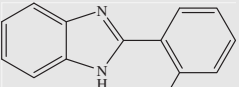
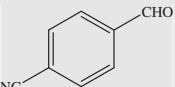
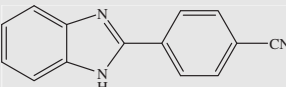
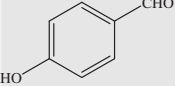
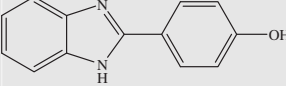
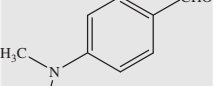
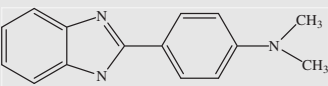
3.1. Typical procedure for the synthesis of 2-aryl-benzimidazoles

A mixture of *o*-phenylenediamine (1 mmol), araldehyde (1 mmol) and amberlite IR-120 (0.20 g) was taken in a 100 ml conical flask. The mixture was mixed well and then irradiated in a domestic microwave oven at 160 W for appropriate time (see Table 1). After which dichloromethane (10 ml) was added to the mixture and left aside for a few minutes, the solid thus separated was recrystallised from methanol or subjected to silica gel column chromatography to get the pure product/s.



Scheme 1

Table 1 Synthesis of 2-aryl-benzimidazoles from araldehydes and *o*-phenylenediamine in the presence of catalytic amount of amberlite IR-120 under solvent-free microwave irradiation.

Entry	Aldehyde (2)	Product (3)	Time (min)	Yield (%)
a			4	92
b			3	95
c			4	92
d			5	90
e			4	89
f			5	85
g			3	95
h			4	90
i			5	85
j			4	84
k			3	88

3a, **3b**, and **3d** were characterized by ¹H NMR spectral analysis, **3a**, **3d**, **3c** and **3k** were characterized by LC-MS spectral analysis, **3e**, **3f**, **3g**, **3h**, **3i** and **3j** were characterized by comparison of their melting points with reported values, and on TLC with authentic samples prepared by the reported methods (Han et al., 2002; Ganesh et al., 2009a,b; Raquel et al., 2009).

5. Conclusion

In conclusion we have presented a rapid, efficient and simple protocol for the synthesis of 2-aryl-benzimidazoles in excellent yields by treating equimolar amounts of aldehydes and *o*-phenylenediamine in the presence of catalytic amount of Amberlite IR-120 under microwave irradiation. The highlighting features of this protocol are its efficiency, selectivity and reusability of the catalyst.

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