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An Expeditious Green Synthesis of Benzimidazoles using VO (acac)$_2$ as Catalyst Under Microwave Irradiation

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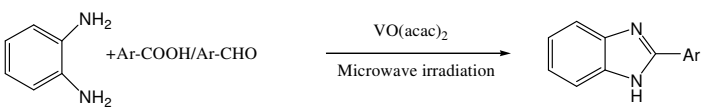
Abstract: Benzimidazoles are considered as a ubiquitous heterocyclic motif and its analogs are used extensively for diverse pharmacological and biological activities. Based on this a series of substituted benzimidazoles has been synthesized from *o*-phenylenediamines and aromatic aldehydes / acids under microwave condition using vanadyl acetylacetonate, VO(acac)$_2$ as catalyst. The condensations have been carried out under solvent-free conditions in compliance with Green Chemistry norms. The heterogeneous reactions conditions provided a very simple, environmentally friendly, clean, economical and selective protocol for the preparation of a number of substituted benzimidazole derivatives. The synthesized benzimidazoles were characterized by comparing their melting points and spectral data with authentic samples. The products were obtained in excellent yields and high purity. The metal catalyzed syntheses of substituted benzimidazoles reaction may proceed through the formation of Schiff's base by condensation of aldehydes with *o*-phenylenediamine and their subsequent oxidative ring closure to give the respective benzimidazole derivatives. Best results in respect of the catalyst were obtained when VO(acac)$_2$ was taken in 5mol%. Lower loading of the catalyst resulted in lower yields and longer reaction time, while higher amount of catalyst did not have much impact on the yields of the products. The absence of either the catalyst or the microwave radiation produced benzimidazoles for some of the products but such reactions required longer reaction times and the yields of the products obtained were also found to be very low.

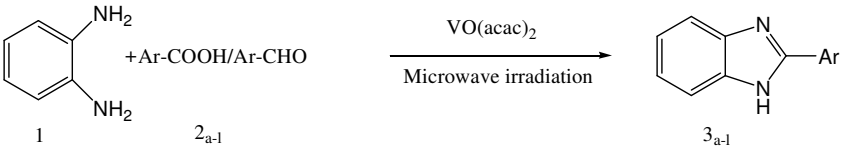


Keywords: vanadyl acetylacetonate, o-phenylenediamine, microwave irradiation, catalysis, environmentally friendly

1. Introduction:

Benzimidazole and its derivatives have acquired a great deal of attention over a past decade or so for exhibiting wide range of biological activities. They are known to act as potent inhibitors of TIE-2 and VEGFR-2 tyrosine kinese receptors, [1] anti-tumor agents, [2] gamma-amino butyric acid (GABA) agonists [3] and 5- HT3 antagonist. [4] Benzimidazoles' role as antimicrobial agents, [5] anti-inflammatory, [6] potential anti-tumor agents [4] and anti-parasitic agents [6] has been well documented. They also act as potential ligand to many transition metals for modeling biological complexes.[7] In view of these remarkable pharmacological activities and potential role as ligand for biological modeled complexes, an overwhelming number of reports on the newer synthesis of benzimidazoles have been registered in the literature. The general method of synthesis of benzimidazoles involves reaction of *o*-phenylenediamine with carboxy aldehydes and carboxy acids [8,9] or their other derivative [10-13] such as chlorides, nitriles and orthoesters with strong acids under high temperatures. Even some of the improved methods that use milder reagents like Lewis acids, [14] inorganic clays [15] or mineral acids[16] suffer from limitations such as drastic reaction conditions, low yields, tedious work-up procedures and co-occurrence of several side products.[17,18] There is also a report of a very tedious and difficult experimental procedure [19] that uses water as the solvent at its critical temperature under high pressure. One of the recent reports [20] indicates that $VO(acac)_2$ can be used as a catalyst for benzimidazoles synthesis particularly if used in combination with other reagents such as $CeCl_3$ or $Ti(OBu)_4$. However, some of the features of this method such as use of environmentally unfavourable chlorinated solvent CH_2Cl_2, long reaction time are not very encouraging. As a consequence, the introduction of newer improved methods to overcome such limitations is still an experimental challenge.

In our continuous effort to design and develop environmentally benign methodologies for catalyst preparation including metal acetylacetonates [21] and organic transformation reactions [22] we wish to report here an alternative protocol for rapid synthesis of pharmacologically important benzimidazoles using catalytic amount of $VO(acac)_2$ under microwave irradiation and solvent free conditions (Scheme 1).



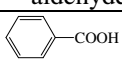
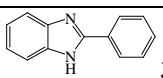
Scheme 1

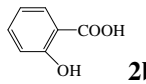
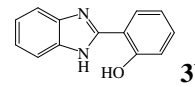
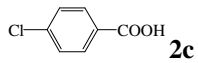
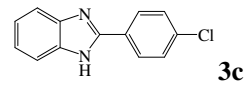
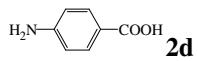
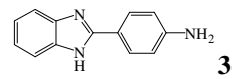
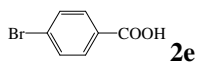
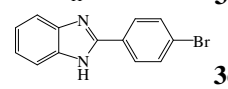
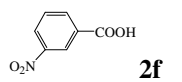
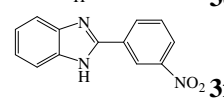
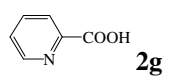
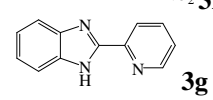
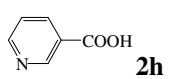
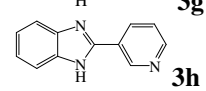
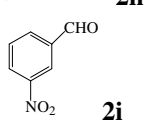
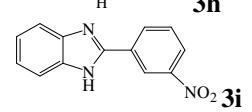
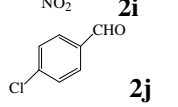
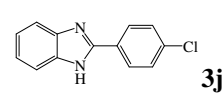
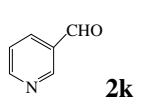
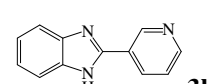
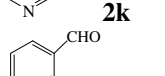
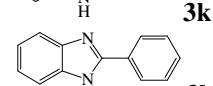
2. Experimental

Melting points were determined in open capillaries and are uncorrected. The completion of reactions was monitored by TLC. IR spectra were recorded on KBr matrix with Perkin Elmer BX-FTIR spectrometer. ^{1}H NMR spectra were recorded in DMSO-d_6 using TMS as internal standard on a 400 MHz Varian spectrometer. Microwave oven equipped with a turntable was used (Godrej 30E BLGX having maximum output of 1000 watt).

In a typical procedure, *o*-phenylenediamine (1 mmol), aromatic acids/ aromatic aldehydes (1.1 mmol) and the catalyst $VO(acac)_2$ (0.05 mmol) were ground together in a pestle mortar. The resulting mixture was irradiated with microwave at a power of 180 watt for short period of time (Table 1). The conversion of the reactants into corresponding benzimidazoles was monitored by TLC. The resulting solid was taken in methanol and the solution was filtered through a short column to remove the little undissolved catalyst. The solution was then dried by evaporation of the solvent through rotary evaporator. The product thus obtained was recrystallized from methanol. All the products were characterized by comparing the melting points and spectral data with authentic samples [23-30].

2.1 Table 1: Reactions of *o*-phenylenediamine with (Ar)-COOH/ (Ar)-CHO in presence of $VO(acac)_2$ under MW irradiation

Entry	Aromatic acid/ aldehyde	Time (min)	Product	Yield (%)[a]	References
1	 **2a**	3.5	 **3a**	91	16

2	 **2b**	2	 **3b**	88	17
3	 **2c**	4	 **3c**	88	16
4	 **2d**	4	 **3d**	85	18
5	 **2e**	4.5	 **3e**	89	19
6	 **2f**	5	 **3f**	87[b]	20
7	 **2g**	3	 **3g**	92	21
8	 **2h**	3	 **3h**	90	22
9	 **2i**	4.5	 **3i**	85[b]	20
10	 **2j**	4	 **3j**	83	16
11	 **2k**	3.5	 **3k**	80	22
12	 **2l**	2.5	 **3l**	88	16

[a] isolated yield. [b] $VO(acac)_2$ required was 10 mol%. The yields of the benzimidazoles were very poor when the reactions were carried out without the catalyst or the MW radiation for the same amount of reaction times.

2.2 *Representative Spectral and Physical Data*

2.2a *2-(4-chlorophenyl)benzimidazole 4d*: mp 288 – 291 °C, IR (KBr): 3041, 1450, 1402, 1280, 965, 750 cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6) δ:

7.10 (m, 2H), 7.30 (d, 2H), 7.60 (d, 2H), 8.20 (d, 2H), 12.5 (s, 1H, NH) ppm.

2.2b *2-(4-hydroxyphenyl)benzimidazole 4e*: mp 221-223 °C, IR (KBr): 3478, 3329, 2929, 1627, 1537, 1036, 815 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 5.20 (s, 1H, OH), 7.30 (s, 2H), 7.50 (d, 2H), 7.80 (m, 2H), 8.20 (d, 2H), 12.10 (s, 1H, NH) ppm.

2.2c *2-(4-N, N-Dimethylaminophenyl)benzimidazole 4f*: mp 282-285 °C, IR (KBr): 3425, 2960, 1575, 1396, 1224, 745 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.10 (s, 6H, CH_3), 6.82 (d, 2H), 7.10-7.13 (m, 2H), 7.48 (d, 2H), 7.97 (d, 2H) ppm.

2.2d *2-(4-methoxyphenyl)benzimidazole 4g*: mp 223-225 °C, IR (KBr): 3478, 2988, 1628, 1536, 1342, 1125, 833 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.25 (s, 3H), 7.52 (br s, 2H), 7.68 (d, 2H), 7.93 (m, 2H), 8.12 (d, 2H), 11.92 (s, 1H, NH) ppm.

2.2e *2-(3-Pyridyl)benzimidazole 4l*: mp 245 – 248 °C, IR(KBr): 1449, 1402, 1280, 746 cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.40(m, 2H), 7.70 (m, 3H,), 8.60 (m, 1H,), 8.75 (d, 1H), 9.35 (d, 1H), 13.05 (s, 1H, NH) ppm.

3. Results and Discussion

As shown in Table 1 aromatic carboxylic acids and aromatic aldehydes react with *o*-phenylenediamine in rather similar fashion to give the corresponding benzimidazoles in very good yields. First, for the optimization of the reaction condition, the effect of catalyst concentration was studied by carrying out the reaction in presence of different amounts of catalyst (5, 10,20mol %). Best results in respect of the catalyst were obtained when $VO(acac)_2$ was taken in 5 mol%. Lower loading of the catalyst resulted in lower yields in longer reaction time, while higher amount of catalyst except for **2f** and **2i** did not increase the product yields significantly in comparable reaction time. The absence of either the catalyst or the MW radiation also produced benzimidazoles for some of the

reactants. But such reactions required longer reaction times and the yields of the products obtained were also very low.

Using the optimized reaction conditions, the substituted benzimidazoles that were obtained were characterized by mp, IR, ^{1}H NMR .The products proceds very cleanly with no undesirable side reactions or products.Thus from the results it may be summarized that the present protocol may be regarded as superior to reported methods in terms of yields, operational simplicity, reaction times and in line with the norms of green chemistry.

4. Conclusions

We have successfully developed an expeditious, facile and efficient catalytic method for the synthesis of substituted benzimidazoles using microwave assisted solvent-free condensation of *o*-phenylenediamine with aromatic aldehydes and/or aromatic acids. The salient feature of this methodology are the mild reaction conditions, high conversions , economic and environmentally friendly, all of which make it a useful and attractive strategy for the preparation of various benzimidazoles simply by changing the substrates.

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