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$VO(acac)_2$ catalyzed condensation of *o*-phenylenediamine with aromatic carboxylic acids/aldehydes under microwave radiation affording benzimidazoles

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Abstract

Vanadyl acetylacetonate, $VO(acac)_2$, has been found to be very effective catalyst for synthesis of a variety of benzimidazoles under solvent-free condition. The methodology involves the exposure of a mixture of *o*-phenylenediamine and a selected aromatic carboxylic acid/aldehyde to microwave radiation without the use of any solvent or supporting agents. The benzimidazoles were obtained in quick time with high yields.

Keywords: Vanadyl acetylacetonate; *o*-Phenylenediamine; Microwave irradiation; Solvent-free

Benzimidazoles have been known to be a very important class of heterocyclic organic compounds [1]. In recent years, this class of organic compounds has garnered a lot of attention, especially due to their applications in various biological studies [2]. Some noteworthy biological activities of benzimidazoles are against several viruses including antimicrobial agents [3], anti-inflammatory [4], potential anti-tumor agents [5] and anti-parasitic agents [4]. They also have wide spread applications in fluorescence, chemo-sensing, crystal engineering and corrosion science [1]. They can also act as ligand to transition metals for modeling biological systems [6].

Thus looking into the spectrum of pharmacological activities along with their potential role as a ligand for biologically modeled transition metal complexes, a number of new methods for the synthesis of benzimidazoles have been discovered and reported [7]. Traditionally, benzimidazoles have most commonly been prepared from the reaction of *o*-phenylenediamine with carboxylic acids under harsh dehydrating reactions, utilizing strong acids [8]. However, though the use of milder reagents, particularly Lewis acids [9], inorganic clay [10] or mineral acids [11] has improved both the yield and purity of this reaction, many of these processes suffer limitations such as drastic reaction condition, low yields, tedious work up procedures and co-occurrence of several side reactions. There is also a report of a very tedious and difficult experimental procedure [12] that uses water as the solvent at its critical temperature under high pressure. One of the recent reports [1] 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

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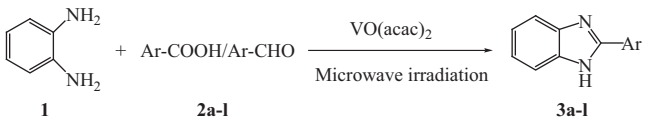

Scheme 1.

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 [13] and organic transformation reactions [14,15], 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).

1. 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 [16–22].

Spectral and physical data of selected compounds: **3a**: Mp 289–291 °C; IR (KBr): 3046, 1444, 1410, 1275, 970, 745 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.7 (s, 1H, NH), 7.95 (m, 2H, C2′-H, C6′-H), 7.25–7.35 (m, 5H, C4-H, C7-H, C3′-H,C4′-H,C5′-H), 7.05 (m, 2H, C5-H, C6-H); **3b**: Mp 182 °C; IR (KBr): 3442, 3320, 2960, 1675, 1478 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.8 (s, 1H, NH), 6.7–7.7 (8H, m), 5.0 (s, 1H, OH) **3c**: Mp 291 °C; IR (KBr): 3041, 1450, 1402, 1280, 965, 750 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6,): δ 12.5 (s, 1H, NH), 8.20 (d, 2H, J = 8.7 Hz, C2′-H, C6′-H), 7.6 (d, 2H, J = 8.4 Hz, C3′-H, C5′-H), 7.30 (d, 2H, C4-H, C7-H), 7.10 (m, 2H, C5-H, C6-H); **3 g**: Mp 219 °C; IR (KBr): 3450, 3050, 1590, 1439, 1310, 1277, 740 cm^{-1}; ^{1}H NMR: 7.18–7.21 (m, 2H), 7.50 (t, 1H, J = 6.50 Hz), 7.60–7.61 (m, 2H), 7.98 (t, 1H, J = 7.70 Hz), 8.31 (d, 1H, J = 7.70 Hz), 8.71 (d, 1H, J = 4.5 Hz), 13.04 (br. 1H); **3 h**: Mp 245–248 °C; IR (KBr): 3068, 1449, 1402, 1280, 746 cm^{-1}; ^{1}H NMR: 13.05 (s, 1H, NH), 9.35 (d, 1H, J = 8.2 Hz, C2′-H), 8.75 (d, 1H, J = 1.8 Hz, C6′-H), 8.60 (m, 1H, C4′-H), 7.70 (m, 3H, C4-H, C7H, C5′-H),7.40 (m, 2H, C5-H, C6-H); **3i**: Mp 309–310 °C; IR (KBr): 3063, 1523, 1444, 1357, 973, 746 cm^{-1}; ^{1}H NMR: 12.9 (s, 1H, NH), 8.90 (s, 1H, C6′-H), 8.50 (d, 1H, J = 6.9 Hz, 64′-H), 8.10 (d, 1H, J = 7.2 Hz, 2′ H), 7.70 (t, 1H, J = 7.2, 6.9 Hz, C3′-H), 7.50 (m, 2H, C4-H) 7.2 (m, 2H, C5-H, C6-H).

2. 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. 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.