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Synthesis of 1,2-disubstitued benzimidazoles using $SiO_2/ZnCl_2$

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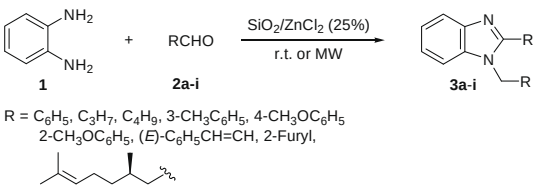
ABSTRACT

A general and easy method for the synthesis of several 1,2-disubstituted benzimidazoles using $SiO_2/ZnCl_2$ and solvent-free conditions is described. This efficient and improved method furnishes selectively and in good yields the corresponding 1,2-bis(organyl)-benzimidazoles starting from *o*-phenylenediamine and aromatic or aliphatic aldehydes. The catalytic system was re-used up three times and the use of focused microwaves accelerates the reaction.

Benzimidazoles and their derivatives exhibit a number of important pharmacological properties, such as antihistaminic,[1] anti-ulcerative,[2] antiallergic,[3] and antipyretic.[4] In addition, benzimidazole derivatives are effective against the human cytomegalovirus (HCMV)[5] and are also efficient selective neuropeptide Y Y1 receptor antagonists.[6] Most of the described methods for the synthesis of benzimidazoles make use of volatile organic solvents and involve solid-phase synthesis via *o*-nitroanilines[7] or the condensation of *o*-phenylenediamines with carboxylic acid derivatives,[8] aldehydes,[9] and aryl halides.[10] Alternatively, the palladium- and copper-catalyzed intramolecular N-arylation starting from *o*-haloanilines has been used.[11] More recently, cleaner protocols have been described, including solvent-free conditions[9a–d] and the use of water[8,9e,f] and ionic liquid as green solvents.[9g] However, most of these protocols use expensive and toxic reagents and/or long reaction times and are limited to aromatic carbonyl compounds. This way, the development of clean, general, and selective routes to benzimidazole, including the use of new catalysts, alternative or non-solvents, renewable starting materials, and non-classical energy sources continues to attract the interest of synthetic organic chemists. The naturally occurring aldehyde, citronellal, besides an important commodity in the flavor and fragrance industry, is a key compound in organic synthesis.[12] In recent times, our group developed new protocols using $SiO_2/ZnCl_2$ as solid-supported catalyst under solvent-free conditions and microwave irradiation to prepare isopulegol and octahydroacridines, starting from (*R*)-citronellal.[13]

In continuation of our studies toward the development of new and cleaner methods for classical synthesis, we report herein the results of the preparation of 1,2-disubstituted benzimidazoles catalyzed by $SiO_2/ZnCl_2$ under solvent-free conditions at room temperature, or under microwave irradiation (MW) (Scheme 1).

Initially, we chose *o*-phenylenediamine (**1a**; 1 mmol) and (*R*)-citronellal (**2a**; 2 mmol) to establish the conditions for the condensation reaction. We examined the temperature, $SiO_2/ZnCl_2$ ratio, and the irradiation with microwaves (MW).[14,15] It was found that when **1a** (1 mmol) was stirred at room temperature in the presence of 0.120 g of $SiO_2/ZnCl_2$ (10%), the reaction proceeded slowly to afford 2-[(*R*)-2,6-dimethylhept-5-enyl]-1-[(*R*)-3,7-dimethyloct-6-enyl]-1*H*-benzo[*d*]imidazole **3a** in 57% yield after 8 h. When the $ZnCl_2$ ratio was increased to 15%, 20%, and 25%, **3a** was, respectively, obtained in 70%, 84%, and 86% yield. The stirring at room temperature for further prolonged time (24 h) or the use of larger amount of the catalytic system (0.240 g) afforded **3a** in comparable yield. Aiming to reduce the reaction time, the mixture was irradiated with focused microwaves (300 W/65 °C, Method B) using a monomode reactor (CEM Explorer). Complete consumption of the starting materials was observed after irradiation for 1.5 min, and **3a** was obtained in 92% yield (Table 1, entry 2). By using conventional heating at 75 °C, stirring for 2 h was necessary inorder to consume the starting materials, and the product was obtained in just 69% yield. The excellent result observed with focused MW



Scheme 1.

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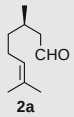
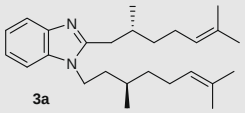
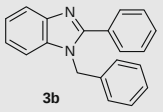
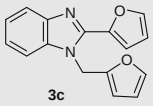
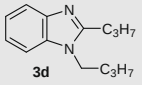
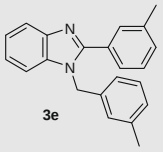
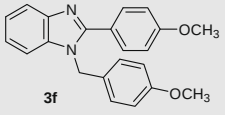
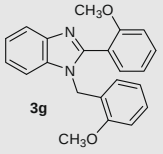
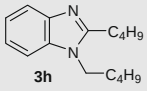
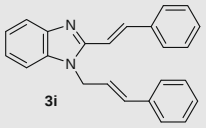
Table 1
Condensation of *o*-phenylenediamine derivatives with aldehydes

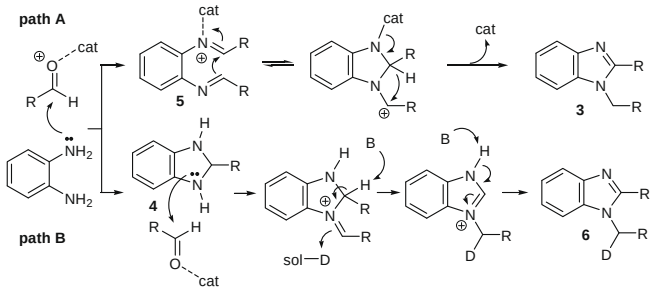
Entry	Aldehydes	Products **3**	Method[a]	Time	Yield[b] (%)
1	 **2a**	 **3a**	A	8 h	86
2	**2a**	**3a**	B	1.5 min	92
3	**2a**	**3**[a]	C	1.5 min	90
4	C_6H_5CHO **2b**	 **3b**	A	20 min	72
5	**2b**	**3b**	B	0.5 min	90
6	**2b**	**3b**	C	0.5 min	87
7	2-Furyl **2c**	 **3c**	A	20 min	75
8	C_3H_7CHO **2d**	 **3d**	A	30 min	78
9	3-$CH_3C_6H_4CHO$ **2e**	 **3e**	A	15 min	82
10	4-$CH_3OC_6H_4CHO$ **2f**	 **3f**	A	15 min	35
11	2-$CH_3OC_6H_4CHO$ **2 g**	 **3g**	A	15 min	40
12	C_4H_9CHO **2 h**	 **3h**	A	30 mim	82
13	(*E*)-$C_6H_5CH{=}CHCHO$ **2i**	 **3i**	A	15 min	65

[a] Method A: the experiments were performed at room temperature. Method B: the experiments were performed under MW irradiation (300 W) using a MW reactor. Method C: the experiments were performed under MW irradiation (420 W) using a domestic MW oven.

[b] Yields of pure products isolated by column chromatography (hexanes/AcOEt). Compounds **3b–i** were identified by mass spectrometry, ^1H, ^{13}C NMR and their spectral data were compared with the literature.[9a,c–e,g]

was also obtained using an unmodified domestic MW oven at a higher power (420 W, Method C, entry 3). When the same protocol was performed at reduced MW power (280 W), the formation of **3a** was observed after a longer reaction time (6 min) in 45% yield. The exclusive formation of the 1,2-disubstituted benzimidazole **3a** was confirmed by analysis of its NMR spectra, including 2D NOESY, COSY, and ^1H–^{13}C HMQC.

Besides the naturally occurring aldehyde **2a**, our protocol was extended to other aldehydes, including aromatic and aliphatic ones. A large difference in the reactivity of unbranched aliphatic



Scheme 2.

and aromatic aldehydes compared with that of citronellal was observed. Aromatic aldehydes, butanal and pentanal reacted almost instantaneously, and the products were isolated after stirring for a few minutes at room temperature (Table 1, entries 4–13).

In almost all the studied cases, the 1,2-disubstituted benzimidazoles **3** were selectively obtained in moderate to good yields. However, when 5-halopyridine-2,3-diamines were employed instead of *o*-phenylenediamines **1**, in the reaction with (*R*)-citronellal **2a**, only a trace amount of the respective condensation product **3** was detected by GC/MS. The main isolated product in these reactions was isopulegol, obtained from the intramolecular ene-cyclization of citronellal.[13a] The solid-supported catalyst was re-used in a new condensation reaction up to three cycles without significant lost of activity. After new treatment with $ZnCl_2$, the supported catalyst was regenerated.[14]

A possible mechanism to explain the formation of the 1,2-disubstituted benzimidazoles **3a–i** from *o*-phenylenediamine **1** and aldehydes **2** is depicted in Scheme 2. Aiming to speculate if the dihydrobenzimidazole **4** was involved, as suggested by Zelenin et al.,[16] we performed the reaction in the presence of deuterated solvents, such as D_2O and CH_3OD (path B). However, any amount of deuterated benzimidazole **6** was detected. This can be indicative that the reaction probably occurs via the path A, with formation of dialkylidene (R = alkyl) or dibenzilidene-*o*-phenylenediamine **5** (R = aryl), followed by 1,3-hydride transfer, according to previous suggestions.[9a,c,f,h]

In conclusion, we have presented here an improved methodology for the selective synthesis of 1,2-disubstituted benzimidazoles by the condensation of *o*-phenylenediamine and aldehydes using solid-supported catalyst. This general, simple, fast, and clean protocol minimizes the organic solvent and energy demands, as well as, the reaction time could be reduced from hours to a few minutes using MW.

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14. The solid-supported catalyst ($SiO_2/ZnCl_2$, 25%) was prepared by the following procedure: To a 100-mL beaker, silica gel 60 (7.5 g), $ZnCl_2$ (2.5 g), and water (3.0 mL) were added. The suspension was stirred for 15 min at room temperature, dried at 80 °C for 3 h and for additional 15 h at 150 °C in an oven and then cooled in a desiccator.
15. *General procedure for the synthesis of benzimidazoles: Method A*: To a mixture of aldehyde (2 mmol) and *o*-phenylenediamine (1 mmol) was added 0.120 g of $SiO_2/ZnCl_2$, and the whole mixture was stirred at room temperature. The reaction progress was followed by TLC. After stirring for 5.0 min–8 h (Table 1), ethyl acetate (10 mL) was added, and the organic solution was separated of the $SiO_2/ZnCl_2$ by filtration. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography over silica gel eluting with hexanes/AcOEt 9:1 mixture, yielding the products. *Method B*: In a typical procedure, aldehydes (2.0 mmol), *o*-phenylenediamines (1 mmol), and the catalyst (0.120 g) were placed in a 10-mL glass tube. The vessel was then sealed with a septum, placed into the microwave cavity and irradiated with stirring under a maximum potency of 300 W for the time given in Table 1. After allowing the mixture to cool to room temperature, the reaction vessel was opened and the product was purified according to that described in Method A. *Method C*: The aforementioned whole mixture was previously stirred for 1 min and then irradiated with microwaves (used a domestic Panasonic model Piccolo NN-S42BK, operating at 2.45 MHz) at 420 W[17] for 0.5–1.5 min (Table 1). The reaction progress was followed by TLC, and the product was purified according to that described in Method A. Compound **3a**: $[\alpha]_D^{20}$ −3.0 (1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71–7.73 (m, 1H); 7.25–7.30 (m, 1H); 7.19–7.23 (m, 2H); 5.06–5.11 (m, 2H); 4.01–4.12 (m, 2H); 2.86 (dd, *J* = 14.8 and 5.6 Hz, 1H); 2.65 (dd, *J* = 14.8 and 8.8 Hz, 1H); 1.68 (s, 3H); 1.67 (s, 3H); 1.59 (s, 6H); 1.03 (d, *J* = 6.0 Hz, 3H); 1.00 (d, *J* = 6.0 Hz, 3H); 1.20–2.24 (m, 12H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 154.3, 143.0, 135.1, 131.9, 131.7, 124.5, 124.4, 122.0, 121.8, 119.4, 109.3, 42.1, 37.5, 37.0, 35.2, 32.7, 30.7, 25.9, 25.8, 25.6, 20.0, 19.8, 17.9. HRMS (ESI): *m*/*z* calcd for $C_{26}H_{40}N_2$ $[M+H]^+$: 381.3270; found: 381.3362.
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17. The oven power was determined according to the method described by: Kingston, H. M. In *Introduction to Microwave Sample Preparation—Theory and Practice*; Jassie, L. B., Ed.; American Chemical Society: Washington, 1988.