One Pot Microwave Promoted Synthesis of 2-Aryl-1*H*-Benzimidazoles Using Sodium Hydrogen Sulfite

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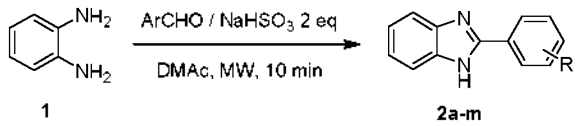
Due the high importance of 2-aryl-1*H*-benzimidazoles for the preparation of biologically active molecules, such as poli(ADP-ribose)phosphorilase inhibitors,[1] Histamine H_4 receptor binders,[2] antiparasitic,[3] cardiovascular,[4] antiulcer,[4] anticancers,[5] antimicrobials,[6] and antihypertensives,[6] their synthesis have received considerable attention. Usually, two different approaches have been performed for the preparation of 2-aryl-1*H*-benzimidazoles: the first one, commonly uses a condensation between *o*-phenylenediamines and benzoic acids,[8] or their derivatives under several conditions,[9] often having the drawbacks of employing strong acidic conditions accompanied by high temperatures. The second one involves the condensation of *o*-diaminoaromatic compounds with widely available aromatic aldehydes in a two-step procedure, which includes an oxidative cyclodehydrogenation of the corresponding aniline Shiff bases intermediates. Several oxidative reagents, such as nitrobenzene (high boiling oxidant/solvent),[10] 1,4-benzoquinone,[11] DDQ,[12] MnO_2,[13] benzofuroxan,[14] tetracyanoethylene,[15] oxone,[16] $Pb(OAc)_4$,[17] $NaHSO_3$,[18a-c] $Na_2S_2O_5$,[19] have been used, but most of them suffers from disadvantages such as laborious workup or purification procedures, long reaction times or produce toxic byproducts, as well as low isolation yields. Other benign oxidants have been employed, like molecular oxygen (low yields and prolonged reaction times, ~ 28 h),[20] I_2/KI/K_2CO_3/H_2O (low yields when aldehydes with electron-donating groups or *ortho* substituted benzaldehydes were used).[21] Recently, sodium dithionite ($Na_2S_2O_4$) has been successfully employed for the one pot preparation of 2-aryl-benzimidazoles by the reduction of *o*-nitroanilines in the presence of benzaldehydes,[22] however, long reaction times (5 h) were needed. An interesting new methodology has been reported which employs H_2O_2/HCl as the oxidant in acetonitrile.[23] Sodium hydrogen sulfite ($NaHSO_3$) has been employed by our group[24] and others[25] for the direct cyclodehydrogenation reaction of substituted 2-aminobenzamides with different benzaldehydes in the preparation of 4(3*H*)-quinazolinones, but despite its use in the preparation of 2-substituted-benzimidazoles has been described,[18a-c] microwave irradiation has never been explored to achieve this reaction in a more efficient way.

This study describes the preparation of thirteen 2-aryl substituted benzimidazole derivatives (**2a-m**) by the microwave promoted reaction between *o*-phenylenediamine **1** and substituted benzaldehydes using sodium hydrogen sulfite in dimethylacetamide (Table 2). The reaction conditions were previously optimized varying the irradiation time and potency level of MW irradiation (Table 1), obtaining the best result for 10 min irradiation (entry 5). With extended irradiation times, several byproducts were observed by TLC analysis and yields



1 **2a-m**

Scheme 1

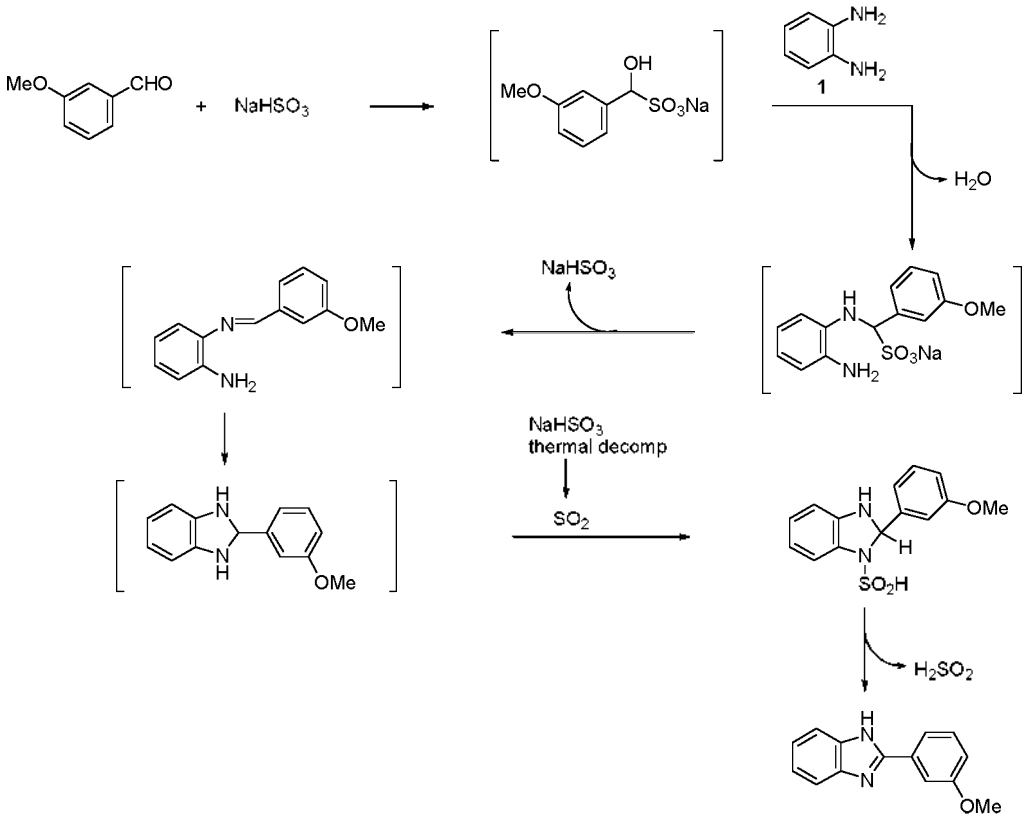
Table 1. Optimization conditions for the preparation of 2-aryl-1*H*-benzimidazol **2a** using $NaHSO_3$ under microwave irradiation

Entry	Potency level of MW irradiation (%)	Time (min)	$NaHSO_3$ (equiv)	Yield (%)
1	50	7	2	40
2	80	7	2	60
3	90	7	2	63
4	50	10	2	52
5	90	10	2	85

Table 2. Synthesis of 2-aryl-1*H*-benzimidazoles using $NaHSO_3$ under microwave irradiation

Compd.	R	Yield (%)[a]	Mp °C (Lit. mp)
2a	3'-OMe	85[b]	210 (210-210.4)[38]
2b	4'-OMe	90	226-228 (227-228)[29]
2c	2'-Cl	90	230-233 (233-234)[30]
2d	2'-OH	62	236-237 (236-237)[31]
2e	2',3'-$(OMe)_2$	72	178-179
2f	4'-F	91	250-252 (250-251)[30]
2g	H	88	290-291 (291-292)[32]
2h	4'-NO_2	99	299-301 (298-300)[31]
2i	3'-NO_2	79	205-206 (204-206)[31]
2j	3'-F	85[c]	220-222
2k	4'-Me	90	274-276 (277-279)[34]
2l	3'-Me	80	213-216 (217-219)[35]
2m	3',4'-$(OMe)_2$	67	232-234 (235.5-236.7)[36]

[a]All yields refer to isolated products. Known compounds were characterized by melting points and ^{1}H NMR. New compounds were fully characterized by NMR, IR, MS and elemental analysis. [b]A test reaction between previously prepared 3-methoxybenzaldehyde-sodium hydrogen sulfite adduct and *o*-phenylenediamine **1**, gave the desired product **2a** in seven minutes, 90% yield. [c]This compound has been previously prepared but its melting point was not reported.[33]



Scheme 2. Proposed mechanism for the synthesis of 2-aryl-1*H*-benzimidazoles using sodium hydrogen sulfite under microwave irradiation

were lowered. Good yields for synthesized compounds were obtained and products were easily isolated after precipitation as solids by cooling the final reaction mixture at room temperature and adding cold water. Compounds **2a-m** (Table 2) were generally obtained in high purity, and recrystallisation from ethanol was only needed in few cases. Irradiation was made at several 30-40 seg stages and monitored by TLC until the starting materials were consumed for the required time. When comparing with previously reported classical thermal conditions using sodium hydrogen sulfite,[18a-c] the developed methodology offers advantages in terms of considerable lowering of the reaction time (~ 3 h), easy of isolation-purification and higher yields. In view the reaction is thought to passed thorough the sodium hydrogen sulfite-aldehyde adduct,[18c] a test reaction was made between the previously prepared hydrogen sulfite-aldehyde adduct[18d] and the *o*-phenylenediamine **1**, which gave the expected benzimidazol **2a** in just 7 minutes (90% yield). Although sodium hydrogen sulfite is a well known reducing agent in organic synthesis and the mechanism for the dehydrogenation step of this reaction has never been described, we suspect the oxidant should be either air-oxygen or sulfur dioxide[26] arising from the thermal decomposition of sodium hydrogen sulfite under heating.[27] A possible mechanism for the double bond formation is postulated on Scheme 2, where the 1,2-dihydro-benzimidazol may react with generated sulphur dioxide to form an adduct which then loss hyposulphurous acid to give the expected 2-aryl-1*H*-benzimidazol.

In conclusion, we have developed a rapid and efficient method for the preparation of 2-aryl-substituted-1*H*-benzimidazole derivatives under microwave irradiation. The improving of reaction times and easy product isolation-purification employing a simple household microwave oven, as well as the use of inexpensive reagents makes this an alternative and attractive method for the organic synthesis of such compounds.

Experimental Section

Melting points were determined in a Fischer-Johns micro hot-stage apparatus and are uncorrected. MW irradiation was made with a GoldStar microwave conventional oven, model MA-690M (600 W, 2450 MHz). NMR spectra were obtained on a JEOL Eclipse Plus spectrometer in hexadeuterated dimethylsulfoxide (DMSO-d_6). ^{1}H NMR were recorded at 400 MHz, ^{13}C NMR at 100 MHz and ^{19}F NMR spectra at 376 MHz. Chemical shifts (δ) are given in ppm *vs.* TMS (^{1}H NMR, ^{13}C NMR) or $CFCl_3$ (^{19}F) used as internal references. Coupling constants are given in hertz. The IR spectra were recorded as KBr discs using a FT-IR Nicolet Magna Spectrometer. Mass spectra (GC-MS) were recorded using a Hewlet Packard 5890 Series I gas chromathograph coupled to a mass detector (EI, 60 eV) Hewlet Packard 5917 A. Elemental analysis of new synthesized compounds were performed by Atlantic Microlab Inc. (Norcross, GA, USA); results fell in the range of ± 0.4% of the required theoretical values. Silica gel plates ALUGRAM® SIL G/UV254 (Macherey-Nagel GmbH & Co., Germany) were used for TLC testing. Reagents were obtained from Aldrich (Milwaukee, MI, USA) or Merck (Darmstadt, Germany) and

used without further purification.

General procedure for the preparation of 2-aryl-1*H*-benzimidazoles (2a-m) using $NaHSO_3$ under microwave irradiation. A mixture of the corresponding *o*-phenylenediamine **1** (1.0 mmol), substituted benzaldehyde (1.1 mmol), sodium hydrogen sulfite (2 equiv) and dimethylacetamide (2 mL) in a 25 mL capped conical flask was put into a teflon cylinder container (5 cm diameter × 15 cm height) and microwave irradiated at several stages (30-40 seg each) to complete the indicated time. After been cooled to room temperature, to the resulting mixture an amount of ice-water was added to precipitate the products (**2a-m**) which were then filtered and washed with cool water, dried under vacuo and recrystallised (from ethanol) when needed. All products were obtained in high purity as indicated by TLC, ^{1}H NMR and elemental analysis.

2-(2,3-Dimethoxyphenyl)-1*H*-benzimidazole (2e): White solid, mp 178-179 °C (ethanol). ^{1}H NMR: δ 12.19 (s, 1H, NH), 7.84 (dd, 1H, J = 7.3 Hz, J = 1.1 Hz, arom-H), 7.64 (m, 3H, arom-H), 7.20 (m, 3H, arom-H), 3.90 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); ^{13}C NMR: δ 153.4, 149.14, 147.4, 143.4, 135.5, 124.9, 124.0, 122.8, 122.1, 121.8, 119.2, 114.8, 112.7, 61.3, 56.6; IR (KBr, cm^{-1}) υ: 3010, 2835, 1603, 1583; EIMS: *m/z* (% rel. int) 254.10 [M^+] (100). Anal Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.64; H, 5.63; N, 11.08.

2-(3-Fluorophenyl)-1*H*-benzimidazole (2j): White solid, mp 220-222 °C (ethanol). ^{1}H NMR: δ 13.00 (s, 1H, NH), 8.02 (d, 1H, J = 7.7 Hz, arom-H), 7.96 (m, 1H, arom-H), 7.69 (m, 1H, arom-H), 7.59 (m, 2H, arom-H), 7.34 (m, 1H, arom-H), 7.23 (m, 2H, arom-H); ^{19}F NMR: δ -112.32; IR (KBr, cm^{-1}) υ: 3053, 2685, 1616, 1582; EIMS: *m/z* (% rel. int) 212.00 [M^-] (100). Anal Calcd for $C_{10}H_9FN_2$: C, 73.57; H, 4.27; N, 13.20. Found: C, 73.42; H, 4.21; N, 13.28.

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