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Acetic acid-promoted condensation of *o*-phenylenediamine with aldehydes into 2-aryl-1-(arylmethyl)-1*H*-benzimidazoles under microwave irradiation

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Abstract: An efficient and simple procedure was developed for the green synthesis of various 2-aryl-1-(arylmethyl)-1*H*-benzimidazoles in high yields by acetic acid-promoted condensation of *o*-phenylenediamine with aldehydes in air under microwave irradiation and transition metal catalyst-free conditions.

Keywords: 2-aryl-1-(arylmethyl)-1*H*-benzimidazoles; *o*-phenylenediamine; aldehydes; microwave irradiation, acetic acid.

INTRODUCTION

The benzimidazole nucleus is of significant importance in medicinal chemistry and many benzimidazole-containing compounds exhibit important biological activities, *i.e.*, as selective neuropeptide YY1 receptor antagonists,[1–4] 5-lipoxygenase inhibitors for use as novel anti-allergic agents,[5] factor Xa (FXa) inhibitors,[6] poly (ADP-ribose) polymerase (PARP) inhibitors,[7] and as human cytomegalovirus (HCMV) inhibitors.[8] In addition, several substituted benzimidazole derivatives have been recently reported to have commercial applications in veterinarian medicine, *i.e.*, as anthelmintic agents, and in diverse human therapeutic areas, such as treatment of ulcers and as antihistaminic.[9] In the light of the affinity they display towards a variety of enzymes and protein receptors, medicinal chemists would certainly classify them as "privileged sub-structures" for drug design.[10] Therefore, the clinical significance of this class of compounds stimulated interest in the synthesis of novel ring systems agents, with retention of the core imidazole moiety.

Traditionally, the synthesis of benzimidazoles involves the condensation of *o*-phenylenediamine with aldehydes,[11–13] and carboxylic acids or their deriva-

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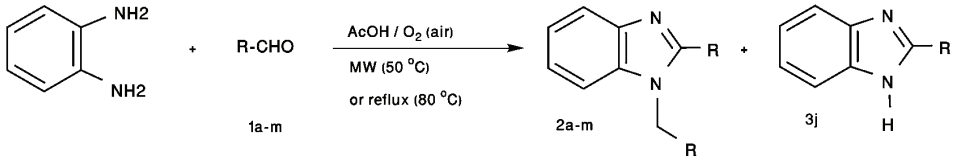
tives (nitriles, amidates, orthoesters) under harsh dehydrating conditions.[14–20] Benzimidazoles have also been prepared on a solid-phase to provide a combinatorial approach.[21,22] The most popular strategies for their synthesis utilize *o*-nitroanilines as intermediates or resort to direct *N*-alkylation of an unsubstituted benzimidazole.[23] A number of synthetic methods that involve intermediate *o*-nitroanilines have evolved to include the synthesis of benzimidazoles on solid supports.[24–29] Another reported approach to these compounds is the reaction of *o*-phenylenediamine with aldehydes in the presence of catalysts under various reaction conditions.[30–41] Recently, a one-pot, solvent-free synthesis of biologically active benzimidazole derivatives using a simple grinding method,[42] and another under heterogeneous catalysis of amberlite IR-120[43] have been reported.

RESULTS AND DISCUSSION

In continuation of previously reported research on the use of acetic acid in various transformations,[44–46] herein, a very simple and selective synthesis of 2-aryl-1-(arylmethyl)-1*H*-benzimidazoles **2a**–**m** by acetic acid-promoted condensation of *o*-phenylenediamine with aldehydes **1a**–**m** both under microwave irradiation and conventional thermal heating in air is reported (Scheme 1, Table I).



Scheme 1. The synthesis of the title compounds.

The structural elucidations of the products were based on their spectral (IR, ^{1}H- and ^{13}C-NMR and mass) data as given below.

*1-Benzyl-2-phenyl-1*H*-benzimidazole (**2a**)*. IR (KBr, cm^{-1}): 3031 (C–H stretching of aromatic ring), 2926 (C–H stretching of aliphatic), 1594 (C=N stretching of imidazole ring), 1549, 1502, 1549, 1448 (C=C stretching of aromatic ring), 1371 (C–N stretching of imidazole ring). ^{1}H-NMR (90 MHz, $CDCl_3$, δ / ppm): 5.34 (2H, *s*, –CH_2–), 7.02–7.28 (15H, *m*, Ar–H). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ / ppm): 47.80, 110.32, 119.41, 122.23, 125.72, 127.31, 128.46, 128.78, 128.80, 129.42, 135.51, 135.84, 142.62, 149.82 (C=N), 153.70. MS (*m*/*z*): 284 (M^+).

*1-(4-Methylbenzyl)-2-(4-methylphenyl)-1*H*-benzimidazole (**2b**)*. IR (KBr, cm^{-1}): 3024 (C–H stretching of aromatic ring), 2930 (C–H stretching of aliphatic), 1623 (C=N stretching of imidazole ring), 1520, 1488 (C=C stretching of aromatic ring), 1284 (C–N stretching of imidazole ring). ^{1}H-NMR (90 MHz, $CDCl_3$, δ / / ppm): 2.45 (3H, *s*, CH_3), 2.51 (3H, *s*, CH_3), 5.53 (2H, *s*, –CH_2–), 7.10–7.95

(12H, *m*, Ar–H). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ / ppm): 21.0, 21.3, 48.2, 110.3, 119.7, 122.5, 122.7, 125.7, 127.0, 128.9, 129.3, 129.5, 133.2, 136.1, 137.4, 139.8, 143.1, 154.2 (C=N). MS (*m*/*z*): 312 (M^+).

TABLE I. Acetic acid-promoted synthesis of 2-aryl-1-(arylmethyl)-1*H*-benzimidazoles

Product[a]	R	Time[b], min	Yield[b,c], %	M.p., °C	
				Found	Reported
2a	C_6H_5	25 (4)	92 (97)	132–134	132[32]
2b	4-MeC_6H_4	60 (6)	64 (82)	126–128	126[32]
2c	4-$MeOC_6H_4$	30 (5)	90 (96)	130–131	131[32]
2d	2-$MeOC_6H_4$	40 (5)	80 (95)	154–155	151[32]
2e	4-HOC_6H_4	30 (7)	60 (85)	250–253	254–256[41]
2f	2-HOC_6H_4	35 (8)	58 (78)	205–208	207–208[41]
2g	4-ClC_6H_4	30 (6)	82 (85)	138–140	137[32]
2h	2-ClC_6H_4	50 (8)	70 (80)	158–159	155[32]
2i	4-$Me_2NC_6H_4$	35 (5)	92 (98)	254–256	252[32]
2j	2-Furyl	50 (5)	70 (75)[d]	96–98	96[32]
2k	4-CNC_6H_4	20 (4)	92 (95)	190–191	187–188[41]
2l	4-$NO_2C_6H_4$	35 (6)	68 (86)	119–120	118[32]
2m	2-$NO_2C_6H_4$	35 (8)	52 (75)	169–170	168–170[33]

[a]The products were characterized by their physical properties and spectral analysis and compared with authentic samples; [b]the reaction times and yields obtained using microwave irradiation are shown in the parenthesis; [c]yield isolated; [d]the product **3j** was isolated in 20 (thermal) and 25 % (microwave irradiation) yields. M.p. 122–124 °C (lit.:[33] 120 °C)

*1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1*H*-benzimidazole (**2c**)*. IR (KBr, cm^{-1}): 3030 (C–H stretching of aromatic ring), 2932 (C–H stretching of aliphatic), 1609 (C=N stretching of imidazole ring), 1538, 1460 (C=C stretching of aromatic ring), 1244 (C–N stretching of imidazole ring). ^{1}H-NMR (90 Mz, $CDCl_3$, δ / ppm): 3.79 (3H, *s*, OCH_3), 3.89 (3H, *s*, OCH_3), 5.34 (2H, *s*, $–CH_2–$), 6.92––7.78 (12H, *m*, Ar–H). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ / ppm): 47.8, 55.2, 55.3, 110.3, 114.2, 114.4, 119.6, 122.5, 122.7, 127.2, 128.4, 130.6, 136.1, 143.2, 154.0 (C=N), 159.1, 160.9. MS (*m*/*z*): 344 (M^+).

*1-(2-Methoxybenzyl)-2-(2-methoxyphenyl)-1*H*-benzimidazole (**2d**)*. IR (KBr, cm^{-1}): 3063 (C–H stretching of aromatic ring), 2961 (C–H stretching of aliphatic), 1600 (C=N stretching of imidazole ring), 1583, 1454 (C=C stretching of aromatic ring), 1258 (C–N stretching of imidazole ring); ^{1}H-NMR (90 MHz, $CDCl_3$, δ / ppm): 3.46 (3H, *s*, OCH_3), 3.64 (3H, *s*, OCH_3), 5.21 (2H, *s*, $–CH_2–$), 6.64––7.81 (12H, *m*, Ar–H). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ / ppm): 43.2, 55.0, 55.1, 109.8, 110.5, 110.6, 119.7, 120.2, 120.6, 121.8, 122.3, 124.3, 127.4, 128.2, 131.3, 132.1, 135.3, 143.1, 152.4 (C=N), 156.3, 157.3. MS (*m*/*z*): 344 (M^+).

*4-{[2-(4-Hydroxyphenyl)-1*H*-benzimidazol-1-yl]methyl}phenol (**2e**)*. IR (KBr, cm^{-1}): 3348 (O–H stretching of phenyl ring), 3002 (C–H stretching of aromatic ring), 2925 (C–H stretching of aliphatic), 1597 (C=N stretching of imidazole

ring), 1515, 1412 (C=C stretching of aromatic ring), 1266 (C–N stretching of imidazole ring). ^{1}H-NMR (90 MHz, DMSO-d_6, δ / ppm): 5.32 (2H, *s*, –CH_2–), 6.78–7.80 (12H, *m*, Ar–H), 9.33 (1H, *brs*, OH), 9.89 (1H, *brs*, OH). MS (*m*/*z*): 316 (M^+).

*2-{[2-(2-Hydroxyphenyl)-1*H*-benzimidazol-1-yl]methyl}phenol* (***2f***). IR (KBr, cm^{-1}): 3384 (O–H stretching of phenyl ring), 3010 (C–H stretching of aromatic ring), 2910 (C–H stretching of aliphatic), 1600 (C=N stretching of imidazole ring), 1460, 1425 (C=C stretching of aromatic ring), 1298 (C–N stretching of imidazole ring). ^{1}H-NMR (90 MHz, DMSO-d_6, δ / ppm): 5.58 (2H, *s*, –CH_2–), 6.18–7.34 (12H, *m*, Ar–H), 9.48 (1H, *brs*, OH), 10.04 (1H, *brs*, OH). MS (*m*/*z*): 316 (M^+).

*1-(4-Chlorobenzyl)-2-(4-chlorophenyl)-1*H*-benzimidazole* (***2g***). IR (KBr, cm^{-1}): 3050 (C–H stretching of aromatic ring), 2920 (C–H stretching of aliphatic), 1546 (C=N stretching of imidazole ring), 1522, 1441 (C=C stretching of aromatic ring), 1346 (C–N stretching of imidazole ring). ^{1}H-NMR (90 MHz, $CDCl_3$, δ / ppm): 5.49 (2H, *s*, –CH_2–), 7.14–8.19 (12H, *m*, Ar–H). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ / ppm): 47.6, 110.3, 120.1, 123.2, 123.4, 127.2, 128.4, 129.1, 129.2, 130.3, 133.7, 134.6, 135.7, 136.2, 142.9, 152.8 (C=N); MS (*m*/*z*): 353 (M^+).

*1-(2-Chlorobenzyl)-2-(2-chlorophenyl)-1*H*-benzimidazole* (***2h***). IR (KBr, cm^{-1}): 3059 (C–H stretching of aromatic ring), 2924 (C–H stretching of aliphatic), 1612 (C=N stretching of imidazole ring), 1512, 1418 (C=C stretching of aromatic ring), 1396 (C–N stretching of imidazole ring). ^{1}H-NMR (90 MHz, $CDCl_3$, δ / ppm): 5.33 (2H, *s*, –CH_2–), 6.57–7.85 (12H, *m*, Ar–H). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ / ppm): 45.6, 110.4, 120.3, 122.4, 123.3, 126.7, 127.0, 127.6, 128.8, 129.4, 129.3, 129.7, 131.2, 132.1, 132.3, 133.2, 134.1, 134.6, 142.8, 151.3 (C=N). MS (*m*/*z*): 353 (M^+).

*1-[4-(Dimethylamino)benzyl]-2-[4-(dimethylamino)phenyl]-1*H*-benzimidazole* (***2i***). IR (KBr, cm^{-1}): 3029 (C–H stretching of aromatic ring), 2912 (C–H stretching of aliphatic), 1590 (C=N stretching of imidazole ring), 1520, 1412 (C=C stretching of aromatic ring), 1348 (C–N stretching of imidazole ring). ^{1}H--NMR (90 MHz, $CDCl_3$, δ / ppm): 2.84 (6H, *s*, NMe_2), 2.92 (6H, *s*, NMe_2), 5.42 (2H, *s*, –CH_2–), 6.68–7.03 (12H, *m*, Ar–H). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ / / ppm): 40.1, 40.4, 48.0, 110.4, 111.6, 112.6, 117.0, 119.1, 122.2, 124.2, 126.7, 130.3, 136.2, 143.0, 149.8, 151.1 (C=N), 155.2. MS (*m*/*z*): 370 (M^+).

*2-(2-Furyl)-1-(2-furylmethyl)-1*H*-benzimidazole* (***2j***). IR (KBr, cm^{-1}): 3020 (C–H stretching of aromatic ring), 2925 (C–H stretching of aliphatic), 1577 (C=N stretching of imidazole ring), 1512, 1470 (C=C stretching of aromatic ring), 1328 (C–N stretching of imidazole ring), 1248 (C–O stretching of furyl ring). ^{1}H-NMR (90 MHz, $CDCl_3$, δ / ppm): 5.60 (2H, *s*, –CH_2–), 6.21–7.60 (10H, *m*, Ar–H). ^{13}C-NMR (22.5 MHz, DMSO-d_6, δ / ppm): 41.6, 108.2, 109.8,

110.0, 110.4, 112.0, 112.8, 119.7, 122.8, 123.2, 135.3, 142.5, 142.9, 143.7, 145.3, 149.5 (C=N). MS (*m*/*z*): 264 (M^+).

*4-{[2-(4-Cyanophenyl)-1*H*-benzimidazol-1-yl]methyl}benzonitrile (**2k**)*. IR (KBr, cm^{-1}): 3061 (C–H stretching of aromatic ring), 2912 (C–H stretching of aliphatic), 2227 (C–N stretching of phenyl ring) 1608 (C=N stretching of imidazole ring), 1504, 1478, 1457 (C=C stretching of aromatic ring), 1386 (C–N stretching of imidazole ring). ^{1}H-NMR (90 MHz, $CDCl_3$, δ / ppm): 5.49 (2H, *s*, $–CH_2–$), 7.21–7.72 (12H, *m*, Ar–H); ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ / ppm): 48.0, 110.2, 111.1, 112.3, 113.7, 117.9, 120.6, 123.5, 124.2, 126.6, 129.6, 132.5, 133.0, 134.1, 135.9, 141.1, 143.1, 151.7 (C=N). MS (*m*/*z*): 334 (M^+).

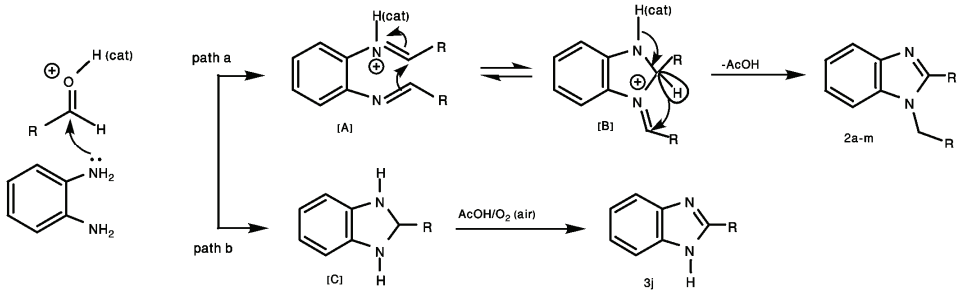
*1-(4-Nitrobenzyl)-2-(4-nitrophenyl)-1*H*-benzimidazole (**2l**)*. IR (KBr, cm^{-1}): 3075 (C–H stretching of aromatic ring), 2926 (C–H stretching of aliphatic), 1614 (C=N stretching of imidazole ring), 1526, 1350 ($–NO_2$ stretching of aromatic ring), 1507, 1445 (C=C stretching of aromatic ring), 1390 (C–N stretching of imidazole ring). ^{1}H-NMR (90 MHz, $CDCl_3$, δ / ppm): 5.50 (2H, *s*, $–CH_2–$), 7.22––8.37 (12H, *m*, Ar–H). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ / ppm): 47.8, 110.2, 120.5, 123.6, 124.0, 124.5, 124.7, 126.6, 130.1, 135.6, 135.8, 142.5, 143.0, 147.5, 148.5, 151.2 (C=N); MS (*m*/*z*): 374 (M^+).

*1-(2-Nitrobenzyl)-2-(2-nitrophenyl)-1*H*-benzimidazole (**2m**)*. IR (KBr, cm^{-1}): 3085 (C–H stretching of aromatic ring), 2964 (C–H stretching of aliphatic), 1611 (C=N stretching of imidazole ring), 1529, 1347 ($–NO_2$ stretching of aromatic ring), 1576, 1459, 1433 (C=C stretching of aromatic ring), 1314 (C–N stretching of imidazole ring). ^{1}H-NMR (90 MHz, $CDCl_3$, δ / ppm): 5.56 (2H, *s*, $–CH_2–$), 6.59–7.64 (12H, *m*, Ar–H). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ / ppm): 45.6, 110.2, 120.3, 123.0, 123.6, 124.8, 125.0, 125.5, 128.2, 128.7, 131.4, 131.8, 133.2, 134.1, 134.6, 143.0, 146.5, 148.7, 149.6 (C=N); MS (*m*/*z*): 374 (M^+).

The ^{1}H- and ^{13}C-NMR spectra of the obtained products are in full consonance with benzimidazole structures and their melting points are in agreement with those reported,[13] (Table I). It was observed that the reactions performed under microwave irradiation were brought to completion in 4–12 min at the 60 % power level. When these reactions were performed under reflux condition at 80 °C for the same time, lower yields of products were obtained, as given in Table I.

A possible mechanism proposed for these reactions is depicted in Scheme 2. This mechanism probably involves an initial acetic acid-promoted condensation of *o*-phenylenediamine with aldehydes **1a**–**m** to yield a di-imine intermediate **A** followed by cyclization to the 2-aryl-1-(arylmethyl)-1*H*-benzimidazoles **2a**–**m** through the intermediate **B** (path a). In order to confirm the involvement of the diarylidene-*o*-phenylenediamine (**A**) as an intermediate, dibenzylidene-*o*-phenylenediamine was prepared separately by the reaction of *o*-phenylenediamine with two equimolar amounts of benzaldehyde in AcOH at 100 °C after 20 min. Microwave irradiation of purely separated dibenzylidene-*o*-phenylenediamine as a

test compound in acetic acid under the same conditions as used for the reactions resulted merely in the formation of 1-benzyl-2-phenyl-1*H*-benzimidazole (**2a**). This can be indicative that the reaction probably occurs *via* path a, with the formation of **A**, followed by 1,3-hydride transfer, according to previous suggestions.[32,36,41,47] However, the formation of 2-(2-furyl)benzimidazole **3j** in minor yield in the case of furylaldehyde (Table I) can be explained possibly through path b involving the formation of dihydrobenzimidazole **C** intermediate followed by dehydrative oxidation in air to yield 2-arylbenzimidazole **3**, as suggested by Xiangming[48] and Zelenin *et al.*[49] A direct oxidative condensation of aldoses with diamines using molecular iodine in AcOH has already been reported for an improved synthesis of aldo-benzimidazoles and aldo-naphthimidazoles, which supports the observations in this work.[50] It is important to emphasize that, when these reactions were conducted under nitrogen atmosphere, no formation of compound **3** was detected and compounds **2a**–**m** were isolated as the sole products in slightly improved yields. This ratifies the role of air in partial oxidation of the intermediate **C** to provide 1*H*-benzimidazole **3j**.



Scheme 2. The suggested mechanism for the formation of the title compounds.

EXPERIMENTAL

Solvents, reagents, and chemical materials were obtained from Aldrich and Merck and purified prior to use. Melting points were determined in open capillary tubes in a Stuart SMP3 apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a JEOL FX 90Q using tetramethylsilane (TMS) as the internal standard. Infrared spectra were recorded on a Perkin Elmer GX FT IR spectrometer (KBr pellets). The microwave-assisted reactions were conducted in a Milstone CombiChem microwave synthesizer. In all irradiation experiments, rotation of rotor, irradiation time, temperature and power were monitored with the "Easy Wave" software package. Benzimidazoles were characterized based on their melting points and IR, ^{1}H- and ^{13}C-NMR spectral data, which were compared with reported data.[32,33,41]

*General procedure for the synthesis of 2-aryl-1-(arylmethyl)-1*H*-benzimidazoles (**2a**–**m**) under microwave irradiation and thermal conditions*

A mixture of *o*-phenylenediamine (0.11 g, 1.0 mmol) and aldehyde **1** (2.0 mmol) dissolved in glacial acetic acid (10 ml) was capped and irradiated in a Milstone CombiChem microwave synthesizer for the appropriate time at 50 °C (Table I). The progress of the reac-

tion was monitored by intermittent rapid cooling of the mixture to r.t. every one minute and analyzing by TLC (*n*-hexane/ethyl acetate, 2:8). After complete conversion of the substrate as indicated by TLC analysis, the solvent was evaporated under reduced pressure to leave the products **2a**–**m** (and **3j**), which were recrystallized from EtOH (96 %) (Table I). Similarly, in a separate set of experiments, these reactions were all repeated in acetic acid under reflux condition at 80 °C (Table I). Their melting points and yields are summarized in Table I.

CONCLUSIONS

In conclusion, the present work offers a simple procedure promoted by inexpensive and non-toxic glacial acetic acid as an efficient methodology for the synthesis of 2-aryl-1-(arylmethyl)-1*H*-benzimidazoles *via* condensation of aromatic aldehydes with *o*-phenylenediamine both under microwave irradiation and conventional thermal heating. A mild, manipulatable procedure, eco-friendly and green aspects avoiding hazardous solvents, shorter reaction times and high yields of the products are the advantages of this method.

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И З В О Д

КОНДЕНЗАЦИЈА *o*-ФЕНИЛЕНДИАМИНА И АЛДЕХИДА ДО 2-АРИЛ-1-(АРИЛМЕТИЛ)--1*H*-БЕНЗИМИДАЗОЛА У ПРИСУСТВУ СИРЋЕТНЕ КИСЕЛИНЕ ПОД УСЛОВИМА МИКРОТАЛАСНОГ ЗРАЧЕЊА

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Развијен је једноставан, ефикасан и еколошки прихватљив поступак за синтезу различитих 2-арил-1-(арилметил)-1*H*-бензимидазола, кондензацијом *o*-фенилендиамина и алдехида у присуству сирћетне киселине под условима микроталасног озрачивања без инертне атмосфере и присуства прелазних метала као катализатора.

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