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A Green, Scalable, One-Minute Synthesis of Benzimidazoles

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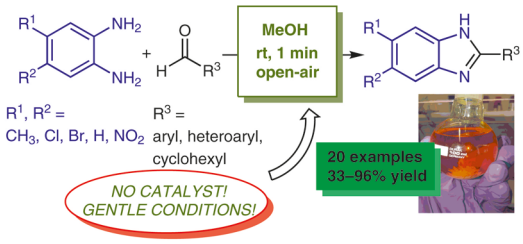

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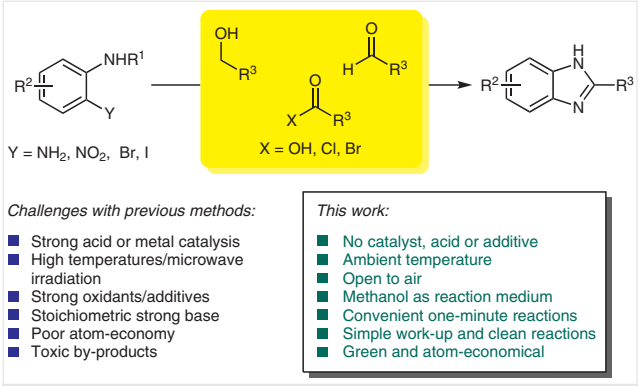
Abstract Herein is reported a substantially improved synthesis of 2-substituted benzimidazoles by condensation of 1,2-diaminoarenes and aldehydes using methanol as the reaction medium. The developed method afforded moderate to excellent yields (33–96%) at ambient temperature, displays high functional group tolerance, is conducted open to air, and requires only one minute reaction time under catalyst- and additive-free conditions. Moreover, the efficient protocol permits scale-up to multi-gram scale synthesis of benzimidazoles and will become a method of choice when constructing such heterocyclic systems.

Key words benzimidazoles, green synthesis, rapid condensation, heterocyclization, 1,2-diaminoarenes, catalyst-free reactions

Benzimidazole is a central heterocyclic structural motif in numerous natural products and a crucial building block in several drug candidates.[1] Benzimidazoles display a range of interesting biological properties such as antiviral,[2] anticancer,[3] antibacterial,[4] anti-inflammatory,[5] antifungal,[6] anti-ulcer,[7] antihypertensive[8] activities. Chemical methods for generating benzimidazoles are numerous in the literature going back as far as 140 years (Scheme 1).[9] Among them, a classical approach involving condensation of diamines and aldehydes is one of the most common methods for the synthesis of 2-substituted benzimidazoles. These reactions are typically conducted at high temperatures over several hours or days at reflux,[10] and in the presence of an added Lewis or Brønsted acid catalyst,[11] metal catalyst,[12,13] or photocatalyst.[14] Despite their efficiency, these methods still employ expensive catalysts, additives and require relatively long reaction times and harsh conditions. The development of even more efficient, environmentally benign and atom-economic methods is desired because of the versatile applications of the benzimidazole heterocycle. We have particularly utilized the condensation between aldehydes and 1,2-diaminobenzenes under catalyst- and additive-free conditions at ambient temperature and with very short reaction times.



Scheme 1 Previous synthetic approaches and challenges

We were struggling to find reports of the use of milder conditions, even though that would be desirable, and were surprised that these mild conditions have not been reported earlier. In this letter, we report on the discovery of these extremely mild and green reaction conditions affording benzimidazoles in medium to excellent yields.

While investigating solvent effects on the benzimidazole formation between equimolar amounts of *o*-phenylenediamine (**1a**) and *p*-nitrobenzaldehyde (**2b**), it was discovered that high conversion was achieved already a few minutes after mixing the reactants in many solvents at ambient temperature. A closer look revealed that one minute was sufficient to achieve full conversion of the starting materials. Concerning solvent effects (Table 1), no product could be observed when using water, whereas ethanol, dioxane, and acetonitrile gave comparably good yields (GC yields of

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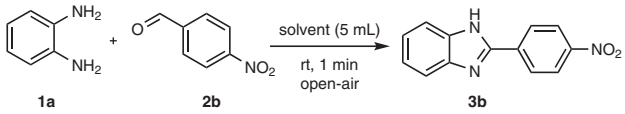
73, 77, and 78%, respectively). Methanol appeared to be a superior solvent for the reaction as 99% GC yield was observed (entry 1) and was therefore further utilized as the medium for studying the generality of this approach. Adding an oxidant, H_2O_2 (entry 4), did not change the outcome in an observable way.

Table 1 Influence of Solvent, Equivalency, and Oxidant on the Chemical Yield of Benzimidazole Formation[a]



1a 2b 3b

Entry	Solvent	Yield (%)[b]
1	MeOH	99
2	EtOH	73
3	H_2O	0
4	MeOH	99[c]
5	dioxane	77
6	MeCN	78
7	MeOH	88[d]
8	MeOH	73[e]
9	MeOH	64[f]

[a] Procedure: To a stirred solution of diamine **1a** (1.0 mmol) in MeOH (5 mL/mmol) was added aldehyde **2b** (1.0 mmol) and stirred at rt for 1 min.
[b] GC yield.
[c] H_2O_2 (1 mmol) was used as oxidant.
[d] 2 Equivalents of aldehyde (2 mmol) were used.
[e] A 10 mL microwave vial was charged with diamine **1a** (1 mmol) and aldehyde **2b** (1 mmol) and the tube was sealed and flushed with N_2. Degassed MeOH (5 mL) was added and the solution stirred at rt for 1 min.
[f] To a stirred solution of diamine **1a** (1 mmol) in MeOH (5 mL) were added aldehyde **2b** (1 mmol) and Na_2CO_3 (0.5 equiv) and stirred at rt for 1 min.

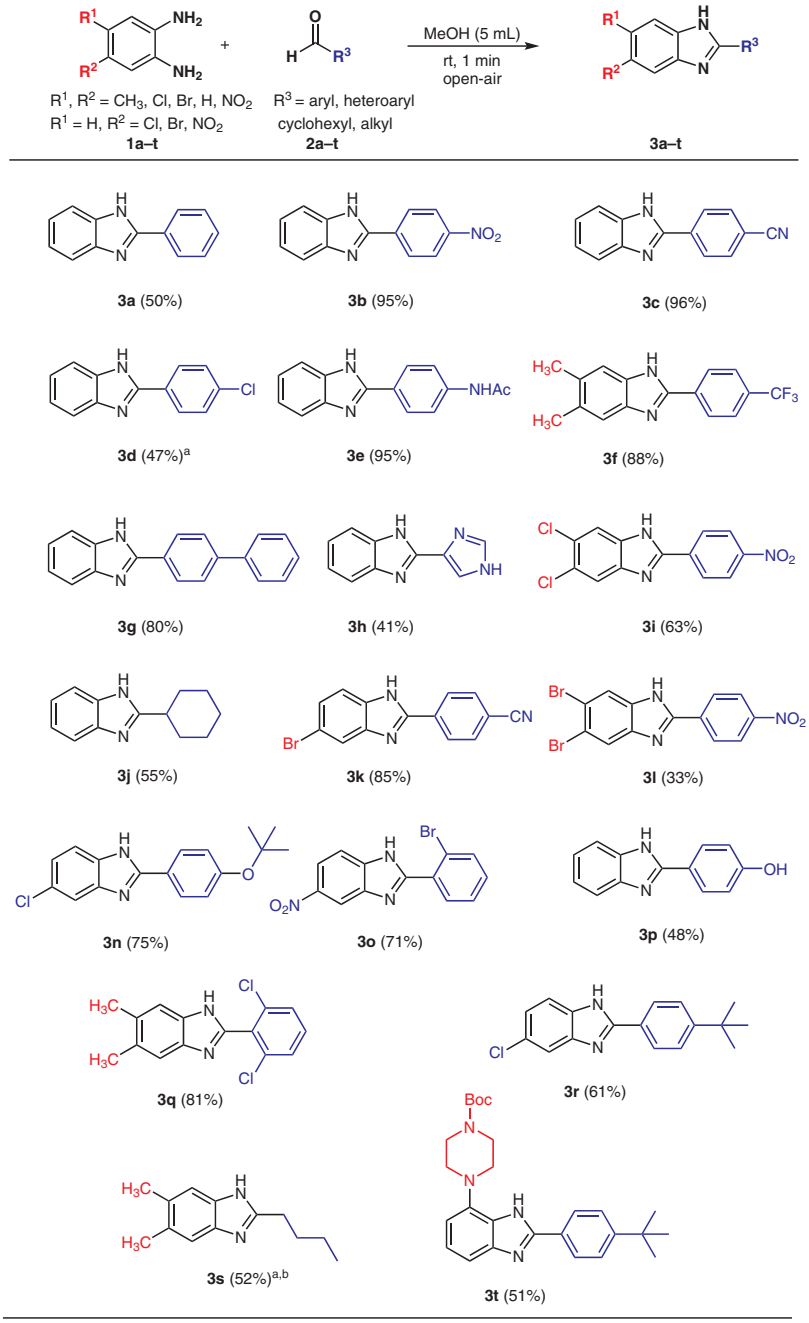
Doubling the equivalents of benzaldehyde led to a drop in the yield by 11% (entry 7). These reaction conditions are remarkably simple and convenient (stir at room temperature and open to air) with a very short reaction time of only one minute.

The rapid rate of conversion to product observed in this reaction prompted us to conduct some control experiments to shed light on the chemistry. The standard reaction between **1a** and **2b** was conducted in a sealed tube under a nitrogen atmosphere and with strictly degassed solvent (entry 8). A reduction in yield from 99 to 73% (GC yield) was observed, thus demonstrating that oxygen is important for the performance of the reaction, likely in the oxidation of the saturated ring-closed intermediate. Another puzzling aspect of the reaction is the absence of an acid or metal catalyst, which is very commonly employed. Activation of the intermediate imine towards nucleophilic attack by the second aromatic amine is usually considered necessary. It is conceivable that small amounts of oxidized aldehydes could be present and effect acid catalysis. Addition of sodium carbonate in order to sequester any minute acid present in solution afforded a diminished yield (64%) of **3b** (entry 9), which may suggest the reaction is enhanced by acid catalysis.

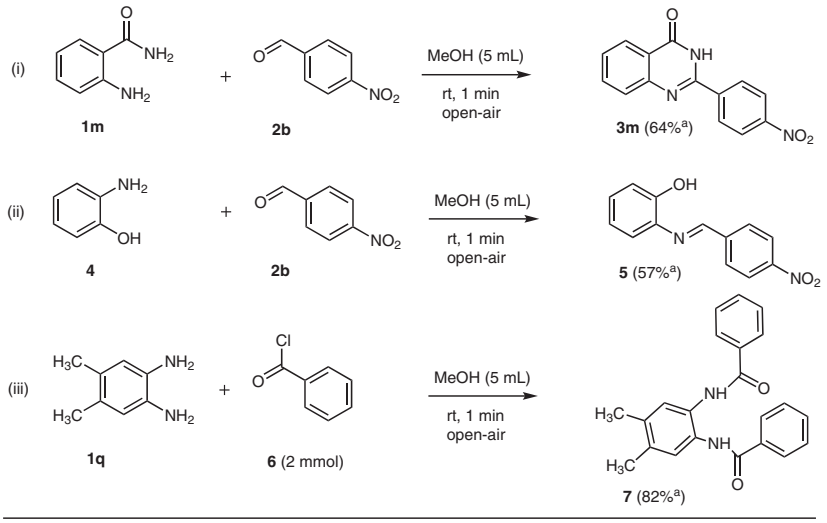
To study the generality of these conditions, a survey of reactions between available substituted phenylenediamines and aryl/alkyl aldehydes was conducted by using the simple conditions found above. The short reaction time of one minute was kept constant in order to demonstrate the rapid reaction performance even though there may be examples in which the conversion was not complete. In the case of unsubstituted phenylenediamine reacting with several *p*-substituted benzaldehydes, moderate to excellent yields were achieved (Scheme 2). Particularly high yields were obtained for *p*-nitro- (**2b**), *p*-cyano- (**2c**), and *p*-acetamido- (**2e**) substituted benzaldehydes (95–96% yield of **3b**, **3c**, and **3e**). The reaction with benzaldehyde (**2a**) afforded 50% yield of **3a** and it was shown by GC–MS that the main remainder was the *N*-alkylated 1,2-disubstituted benzimidazole – a known by-product in this synthesis. In the case of *p*-chlorobenzaldehyde (**2d**) a moderate 47% yield was obtained of the expected benzimidazole **3d**. GC–MS analysis of the reaction mixture revealed that the *N*-4-chlorobenzyl-1,2-substituted benzimidazole was formed with 45% conversion (GC). The *N*-benzylated by-products likely arise from double imine formation followed by a Cannizzaro-like hydride transfer to saturate the benzylic carbon.[15] *p*-Hydroxybenzaldehyde (**2p**) afforded moderate 48% yield of benzimidazole **3p**. Here, the unreacted starting material was the majority of the remainder. The heterocyclic aldehyde **2h** gave moderate 41% yield of the desired product **3h**. *p*-Phenyl benzaldehyde (**2g**) gave high yield of benzimidazole **3g** (80%).[16] Aliphatic aldehydes were also demonstrated to work in the reaction through cyclohexyl aldehyde (**2j**) which afforded the 2-cyclohexylbenzimidazole **3j** in 55% yield. In the case of linear aldehyde **2s**, we obtained both the desired 2-substituted benzimidazole **3s** (52% NMR yield) and 1,2-disubstituted benzimidazoles (in overall 78% yield).

Next, substituted phenylenediamines were tested with various aldehydes. A series of 4-substituted phenylenediamines with bromo- (**1k**), chloro- (**1n**), and nitro- (**1o**) substituents were employed with various aldehydes to generate substituted 2-arylbenzimidazoles **3k**, **3n**, **3o**, and **3r** in very good yields (71–85%). Simultaneous variations on the aldehyde substituent revealed that the reaction is compatible with both π-donor (*tert*-butoxy) and π-acceptor (cyano) substituents in the *para* position of the aryl group, and even an *ortho*-bromo substituent was well tolerated. The 4,5-dimethyl-substituted phenylenediamine gave high yields of **3f** (88%) and **3q** (81%) and showed compatibility with the electron-withdrawing trifluoromethyl group on the aldehyde. The *ortho*-disubstituted 2,6-dichlorobenzaldehyde demonstrates the steric tolerance at these positions. Markedly lower yields were obtained with the 4,5-dihalogenated phenylenediamines **1i** and **1l** which afforded the 2-(*p*-nitro-

phenyl) benzimidazoles **3i** and **3l** in 63% and 33% yield, respectively. It has been assumed that lowered yields are mainly caused by unreacted starting materials or formation of the benzylated benzimidazole by-product. A more thorough analysis of the formation of **3l** revealed that the yield is likely low because of solubility issues with the reactants, and longer reaction times (1–25 min) or increased temperature (rt to 70°C) did not improve the yield. Finally, we have used a more complex diamine **1t** to generate 4-(*N*-Boc-piperazinyl) benzimidazole **3t** in 51% yield (Scheme 2). This represents a formal synthesis of a Gonadotropin-releasing hormone receptor antagonist.[17] The previously reported method required 48 hours under reflux, whereas our conditions yield the target benzimidazole **3t** in one



Scheme 2 Synthesis of substituted benzimidazoles – scope and limitations. General procedure: To a stirred solution of diamine **1a–t** (1.0 mmol) in MeOH (5 mL) was added aldehyde **2a–t** (1.0 mmol) and stirred at rt for 1 min; isolated yields are given. [a] In addition to the desired product *N*-alkyl-substituted 1,2-disubstituted benzimidazole was observed as by-product (GC). [b] NMR yield.



Scheme 3 (i) Formation of quinazolinone from the reaction with 2-aminobenzamide. (ii) Formation of imine in reaction with 2-aminophenol. (iii) Formation of bis-acylation product in the reaction with benzoyl chloride. Procedures: (i) To a stirred solution of diamine **1m** (1 mmol) in MeOH (5 mL) was added aldehyde **2b** (1 mmol) and stirred at rt for 1 min. (ii) To a stirred solution of aminophenol **4** (1 mmol) in MeOH (5 mL) was added aldehyde **2b** (1 mmol) and stirred at rt for 1 min. (iii) To a stirred solution of diamine **1q** (1 mmol) in MeOH (5 mL) was added acid chloride **6** (1 mmol) and stirred at rt for 1 min. [a] Isolated yield.

minute in good yield. Overall, the studies herein demonstrate that the remarkably practical and mild reaction conditions appear to be general for the reaction.

On the basis of the scope study, it was postulated that the reaction conditions could also favor similar heterocyclizations in other dinucleophile systems reacting with aldehydes.

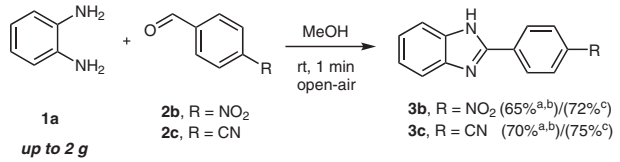
Therefore, 2-aminobenzamide (**1m**) was employed as the dinucleophile source with *p*-nitrobenzaldehyde (Scheme 3i). The reaction afforded quinazolinone **3m** in 64% isolated yield. This demonstrates that such simple reaction conditions can potentially be employed more generally or should at least be tested when similar condensations are conducted. A reaction between 2-aminophenol and 4-nitrobenzaldehyde afforded the imine **5**, which could be isolated in 57% yield (Scheme 3 ii). This observation supports that the first stage of the mechanism is likely imine formation. Furthermore, we tested the reaction conditions with carboxylic acid derivatives. No reaction occurred with phenylenediamine and benzoic acid, whereas with benzoyl chloride **6** and diamine **1q** (Scheme 3 iii), the reaction afforded diamide **7** in 82% yield. These compounds could be important intermediates for various heterocyclic systems.[18]

In order to further probe the applicability of our reaction conditions, two reactions were conducted at up to 2 g scale. *p*-Nitro- (**2b**) and *p*-cyanobenzaldehyde (**2c**) produced the anticipated benzimidazoles **3b**[19] and **3c** in 65 and 70% isolated yield, respectively (Scheme 4). Both products were crystallized from the reaction mixture after work-up and did not require further purification.

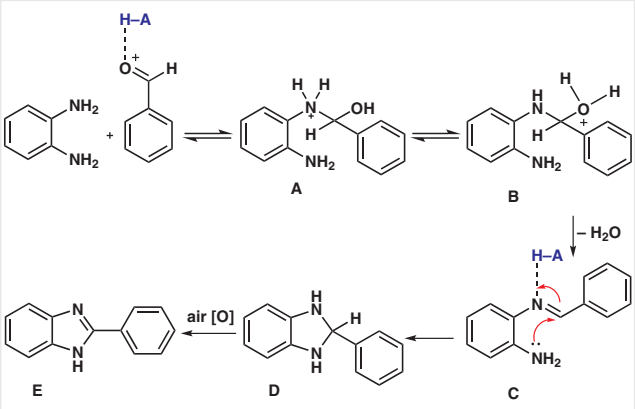
Although the yields are diminished compared to those of the small-scale reactions, they are still high. GC–MS analysis of the reaction mixture revealed that 72% of **3b** and 75% of **3c** were formed and the remainder was mainly unreacted substrates.

On the basis of literature studies and the experimental results, a mechanism is proposed for obtaining 2-arylbenzimidazoles as shown in Scheme 5. The first step involves the acid-catalyzed condensation reaction between amine and aldehyde to form imine intermediate (**C**) via (**B**) by loss of water. Subsequent cyclization gives intermediate **D**, followed by air oxidation to obtain the observed product (**E**).

In summary, we have re-discovered a classical heterocyclization reaction between phenylenediamines and aldehydes to generate benzimidazoles utilizing extremely simple, practical, and green conditions without the explicit addition of any acid- or metal catalyst. The simplicity of the



Scheme 4 Multi-gram scale synthesis of benzimidazoles. Procedure: To a stirred solution of diamine **1a** (18.5 mmol) in MeOH (50 mL) was added aldehyde **2b** or **2c** (18.5 mmol) and stirred at rt for 1 min. [a] After the reaction time, H_2O (30 mL) was added and the mixture was diluted with EtOAc (60 mL). The reaction solution was kept at rt for some time. Crystals slowly formed and were finally filtered off to obtain the desired benzimidazole derivatives **3b** (dark-brown crystals) and **3c** (yellow crystals). [b] Isolated yield. [c] GC yield.



Scheme 5 A likely reaction mechanism with general acid catalysis

conditions is remarkable and this should become a method of choice for *de novo* synthesis of a range of benzimidazoles.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690797. Included are detailed procedures, characterization data, and NMR spectra.

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(16) **2-([1,1'-Biphenyl]-4-yl)-1H-benzo[d]imidazole (3g); Typical Procedure**

In a 25 mL round-bottomed flask, diamine **1g** (100 mg, 0.93 mmol) was dissolved in MeOH (5 mL). To the stirred solution was added aldehyde **2g** (169 mg, 0.925 mmol) and it was stirred for 1 min at rt. Then, the reaction was quenched with water (10 mL), diluted with EtOAc (50 mL), and washed with water (30 mL). The water layer was extracted with EtOAc (2 × 30 mL). The organic layers were combined and dried with anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent was evaporated under reduced pressure. The crude product was further isolated by using flash chromatography (EtOAc/*n*-pentane, 20:80) to obtain compound **3g** as a yellow solid. Yield: 200 mg (80%); R_f = 0.48 (EtOAc/*n*-pentane, 30:70). ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.58 (s, 1 H), 7.99–7.92 (m,

2 H), 7.70–7.64 (m, 2 H), 7.64–7.57 (m, 2 H), 7.36 (dd, *J* = 8.4, 6.9 Hz, 2 H), 7.31–7.22 (m, 1 H), 7.02 (dd, *J* = 7.8, 1.4 Hz, 1 H), 6.87 (td, *J* = 7.6, 1.4 Hz, 1 H), 6.66 (dd, *J* = 8.0, 1.4 Hz, 1 H), 6.50 (td, *J* = 7.5, 1.4 Hz, 1 H). ^{13}C NMR (101 MHz, acetone-d_6): δ = 156.6, 144.7, 129.8, 129.7, 128.5, 128.3, 127.8, 127.6, 117.6, 117.5, 115.6. HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{15}N_2^+$: 271.1230; found: 271.1232.

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(19) **Gram-Scale Synthesis of 2-(4-Nitrophenyl)-1*H*-benzo[d]imidazole (3b)**

In a 250 mL round-bottomed flask, benzene-1,2-diamine **1b** (2.00 g, 18.5 mmol) was dissolved in MeOH (50 mL). To the stirred solution was added 4-nitrobenzaldehyde **2b** (2.80 g, 18.5 mmol) and it was stirred for 1 min at rt. Then, the reaction was quenched with water (40 mL) and diluted with EtOAc (50 mL). After a while, crystals were formed in the reaction mixture at rt. The crystals were filtered off and dried to obtain compound **3b** as dark-brown crystals. Yield: 2.85 g (65%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.83 (s, 1 H), 8.40–8.30 (m, 2 H), 8.34–8.22 (m, 2 H), 7.24 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.03 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1 H), 6.76 (dd, *J* = 8.1, 1.4 Hz, 1 H), 6.63–6.53 (m, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 153.5, 148.3, 144.9, 142.4, 133.9, 129.4, 128.8, 123.9, 117.0, 116.0, 115.1. HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{13}H_8N_3O_2^-$: 238.0622; found: 238.0623.